PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 217/26, A61K 31/47, C07D 401/12, 409/12, 401/04, 401/06, 405/04, 405/06, 491/04, 413/04, 401/10, 405/12 // (C07D 491/04, 317:00, 221:00)

A1

(11) International Publication Number: **WO 98/38168**

(43) International Publication Date: 3 September 1998 (03.09.98)

(21) International Application Number: PCT/JP98/00715

(22) International Filing Date: 23 February 1998 (23.02.98)

(30) Priority Data:
9/44408 27 February 1997 (27.02.97) JP

(71) Applicant *(for all designated States except US)*: TANABE SEIYAKU CO., LTD. [JP/JP]; 2–10, Dosho–machi 3–chome, Chuo–ku, Osaka–shi, Osaka 541–0045 (JP).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: UKITA, Tatsuzo [JP/JP]; 6–611–202, Koyo–cho–naka 6–chome, Higashinada–ku, Kobe–shi, Hyogo 658–0032 (JP). OMORI, Kenji [JP/JP]; 33–1, Miyagadani–cho, Takatsuki–shi, Osaka 569–1023 (JP). IKEO, Tomihiro [JP/JP]; 286–13, Nishin–cho 3–chome, Omiya–shi, Saitama 331–0044 (JP).

(74) Agents: AOYAMA, Tamotsu et al.; Aoyama & Partners, IMP Building, 3–7, Shiromi 1–chome, Chuo–ku, Osaka–shi, Osaka 540–0001 (JP).

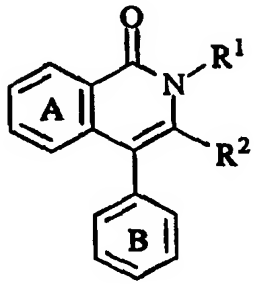
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: ISOQUINOLINONE DERIVATIVES, PROCESS FOR PREPARING THE SAME, AND THEIR USE AS PHOSPHODIESTERASE INHIBITORS

(57) Abstract

An isoquinolinone derivative of formula (I) wherein Ring A and Ring B are substituted or unsubstituted benzene, R^1 is (1) H, (2) substituted or unsubstituted lower alkyl, (3) substituted or unsubstituted cyclo–lower alkyl, (4) substituted or unsubstituted aryl, (5) substituted or unsubstituted heterocycle, or (6) amino optionally having one or two substitutents, R^2 is $-COOR^3$ or $-CON(R^4)(R^5)$, R^3 is H or ester residue, and $-N(R^4)(R^5)$ is substituted or unsubstituted nitrogen–containing aliphatic heterocycle or substituted or unsubstituted amino, provided that when R^1 is H or substituted or unsubstituted lower alkyl, then at least one of Ring A and Ring B is benzene being substituted by two or more lower alkoxy, or a pharmaceutically acceptable salt thereof, these compounds showing cGMP–specific PDE inhibitory activity, especially, selective phosphodiesterase V (PDEV) inhibitory activity, and hence, being useful for the prophylaxis or treatment of various diseases such as chronic heart failure, angina, pulmonary hypertension, erectile dysfunction, etc.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

DESCRIPTION

ISOQUINOLINONE DERIVATIVES, PROCESS FOR PREPARING THE SAME, AND THEIR USE AS PHOSPHODIESTERASE INHIBITORS

TECHNICAL FIELD

The present invention relates to a novel isoquinolinone derivative exhibiting a cGMP specific phosphodiesterase (PDE) inhibitory activity (PDE V inhibitory activity) and being useful as a medicament, a process for preparing the same, and an intermediate therefor.

BACKGROUND ART

In general, it is known that cGMP, which is an intracellular second messenger, is decomposed and inactivated by phosphodiesterase (abbreviated as "PDE") which widely distributes in many cell types and tissues of the living body, and when said PDE activity is inactivated, the level of cGMP in tissue cells is increased, and as a result, various pharmacological activities, for example, relaxation of vascular smooth muscle and bronchial smooth muscle is exhibited.

Moreover, such cGMP specific PDE inhibitors (i.e., PDE V inhibitors) can show inhibition of platelet aggregation and vasodilating activity, etc. [cf. C. D. Nicholson, et al., Trends in Pharmacological Sciences, **12**, 19-27, 1991]. Therefore, PDE V inhibitors are considered to be useful in the treatment of various diseases, such as bronchial asthma, thrombosis, depression, central hypofunction after cerebrovascular obstruction, cerebrovascular dementia, and heart failure.

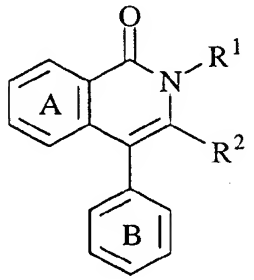
Recently, a fused pyridazine compound having the above-mentioned

PDE V inhibitory activity, etc. has been known to be useful in the prophylaxis or treatment of hypertension, angina, myocardial infarction, chronic or acute heart failure, pulmonary hypertension, etc. (cf., PCT Patent Publication WO 9605176, etc.). Moreover, it has been also reported that 1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl]phenyl-sulfonyl]-4-methylpiperazine [general name: Sildenafil] is useful in the treatment of diseases such as penile erectile dysfunction (copulative impotence), etc. (cf., Boolell, M. et al., Journal of Urology, **155**, 5, p. 495A (1996); Terrett N. K. et al, Bioorganic & Medicinal Chemistry Letters, **6**, 15, p. 1819-24 (1996); and Ballard S. A. et al., British Journal of Pharmacology, **118**, p. 153 (1996)).

DISCLOSURE OF INVENTION

An object of the present invention is to provide a novel isoquinolinone derivative showing an excellent selective PDE V inhibitory activity. Another object of the present invention is to provide a process for preparing a novel isoquinolinone derivative. Still further object of the present invention is to provide an intermediate for preparing the same.

The present invention relates to an isoquinolinone derivative of the formula (I):



(I)

wherein Ring A and Ring B are the same or different and each a substituted or unsubstituted benzene ring, R^1 is (1) a hydrogen atom, (2) a substituted or

unsubstituted lower alkyl group, (3) a substituted or unsubstituted cyclo-lower alkyl group, (4) a substituted or unsubstituted aryl group, (5) a substituted or unsubstituted heterocyclic group, or (6) an amino group optionally having one or two substituents, R^2 is a group of the formula $-COOR^3$ or $-CON(R^4)(R^5)$, R^3 is a hydrogen atom or an ester residue, and a group of the formula $-N(R^4)(R^5)$ is a substituted or unsubstituted nitrogen-containing aliphatic heterocyclic group or a substituted or unsubstituted amino group, provided that when R^1 is a hydrogen atom or a substituted or unsubstituted lower alkyl group, then at least one of Ring A and Ring B is a benzene ring which is substituted by two or more lower alkoxy groups, or a pharmaceutically acceptable salt thereof.

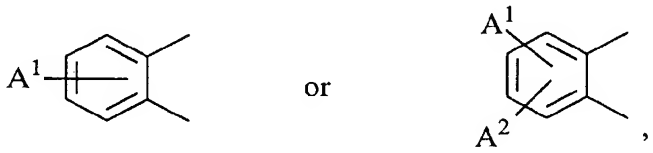
Among the compounds (I) of the present invention, a group of the formula $-COOR^3$ is ones wherein R^3 is a hydrogen atom, or an ester residue such as an aryl-lower alkyl group (e.g., benzyl, nitrobenzyl, a protected or unprotected amino-benzyl, a lower alkoxybenzyl), a lower alkyl group (e.g., methyl, ethyl, propyl, butyl), a cyclo-lower alkyl group (e.g., cyclopentyl), or a tri-lower alkylsilyl-lower alkyl group (e.g., trimethylsilylmethyl, tert-butyl-dimethylsilylmethyl). When R^2 is a group $-CON(R^4)(R^5)$, a group of the formula $-N(R^4)(R^5)$ is, for example, a substituted or unsubstituted nitrogen-containing 5 or 6-membered aliphatic heterocyclic group (e.g., a hydroxy-lower alkyl-substituted piperazinyl group, a morpholino group, a pyrrolidinyl group, a piperidinyl group), or a substituted or unsubstituted amino group (e.g., an imidazolyl-substituted lower alkylamino group, a mono- or di-lower alkylamino group, amino group).

Ring A and Ring B of the compounds (I) of the present invention are a

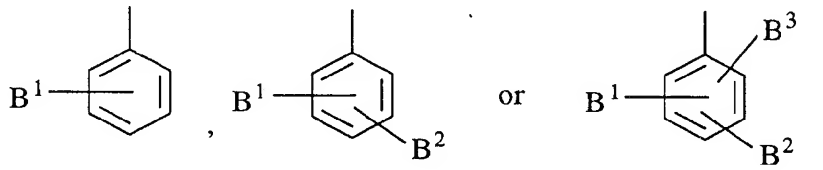
benzene ring which may optionally have 1 to 4 substituents being the same or different, and such substituents of said Ring A and Ring B are, for example, a protected or unprotected hydroxy group, a lower alkylenedioxy group, a halogen atom, a lower alkyl group, a mono- or di-lower alkylcarbamoyloxy group, or a group of the formula R^6–$(CO)_n$–O– (R^6 is a substituted or unsubstituted lower alkyl group, a substituted or unsubstituted lower alkenyl group, a substituted or unsubstituted cyclo-lower alkyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted arylsulfonyl group, or a substituted or unsubstituted heterocyclic group, and n is 0 or 1).

More particularly, Ring A of the compound (I) of the present invention is a benzene ring which may optionally have 1 to 4 substituents being the same or different, and such substituents of Ring A are, for example, a protected or unprotected hydroxy group, a lower alkylenedioxy group, a halogen atom, a lower alkyl group, a mono- or di-lower alkylcarbamoyloxy group, or a group of the formula of the formula R^6–$(CO)_n$–O– (R^6 is a substituted or unsubstituted lower alkyl group, a substituted or unsubstituted lower alkenyl group, a substituted or unsubstituted cyclo-lower alkyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted arylsulfonyl group, or a substituted or unsubstituted heterocyclic group, and n is 0 or 1). Ring B of the compound (I) of the present invention is a benzene ring which may optionally have 1 to 4 substituents being the same or different, and such substituents of Ring B are, for example, a protected or unprotected hydroxy group, a lower alkoxy group, a lower alkyl group, a halogen atom, or a lower alkylenedioxy group.

The suitable examples of Ring A and Ring B of the compounds of the present invention are these wherein Ring A is a benzene ring of the formula:



and Ring B is a benzene ring of the formula:



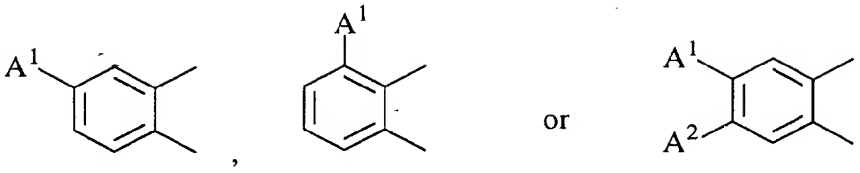
wherein A^1 and A^2 are the same or different and each a member selected from a hydrogen atom, a protected or unprotected hydroxy group, a lower alkylenedioxy group, a halogen atom, a lower alkyl group, a mono- or di-lower alkylcarbamoyloxy group, and a group of the formula R^6–$(CO)_n$–O– (R^6 and n are the same as defined above), B^1, B^2 and B^3 are the same or different and each a member selected from a protected or unprotected hydroxy group, a lower alkoxy group, a lower alkyl group, a halogen atom and a lower alkylenedioxy group.

When Ring A and/or Ring B have a substituent of the formula R^6–$(CO)_n$–O–, R^6 is, for example, (1) a lower alkyl group which may optionally be substituted by 1 to 2 groups selected from a 5- to 10-membered heteromonocyclic or heterobicyclic group being optionally substituted by 1 to 4 groups selected from a hydroxy-substituted lower alkyl group, a lower alkyl group, an oxo group and a lower alkoxycarbonyl group; a 6- to 10-membered monocyclic

or bicyclic aryl group being optionally substituted by 1 to 4 groups selected from a lower alkylenedioxy group, a carboxyl group, a lower alkoxycarbonyl group, a lower alkoxy group, a sulfamoyl group, a carbamoyl group, a nitro group, a protected or unprotected amino group, a phenyl group, a halogen atom, a mono-lower alkylamino group, a di-lower alkylamino group, a lower alkyl-piperazinocarbonyl group, a hydroxy-substituted lower alkyl group and a lower alkyl group; a cyano group; a carboxyl group; a mono- or di-lower alkylamino group; a lower alkoxy-substituted lower alkoxy group; a lower alkoxy group; a hydroxy group; a carbamoyl group; a lower alkoxycarbonyl group; a cyclo-lower alkyl group; and a benzoyl group, or (2) a 5- to 10-membered heteromonocyclic or heterobicyclic group which may optionally be substituted by 1 to 4 groups selected from a lower alkyl group, a cyano group, a carboxyl group, a mono- or di-lower alkylamino group, a lower alkoxy-substituted lower alkyl group, a hydroxy group, a lower alkoxy group, a carbamoyl group, a lower alkoxycarbonyl group and a nitro group.

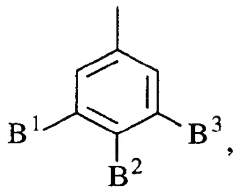
The 6- to 10-membered monocyclic or bicyclic aryl group is, for example, a phenyl group, a naphthyl group, etc., and the 5- to 10-membered heteromonocyclic or heterobicyclic group is, for example, a pyridyl group, a pyrimidinyl group, a pyrazinyl group, a piperidyl group, a piperazinyl group, a pyrrolidinyl group, an isoquinolyl group, a quinolyl group, a tetrazolyl group, a thienyl group, a furyl group, a morpholino group, a pyrrolyl group, a benzimidazolyl group, an imidazolyl group, a quinazolyl group, a phthalazinyl group, etc.

Among Ring A and Ring B, more preferable examples of Ring A are a benzene ring of the formula:



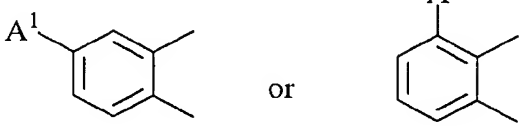
or

and more preferable examples of Ring B are a benzene ring of the formula:.

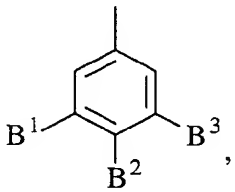


wherein A^1, A^2, B^1, B^2 and B^3 are the same as defined above.

Besides, among Ring A and Ring B, the most preferable examples of Ring A are a benzene ring of the formula:



or , and the most preferable examples of Ring B are a benzene ring of the formula:



wherein A^1, A^2, B^1, B^2 and B^3 are the same as defined above.

Suitable examples of the substituents (A^1 and A^2) of Ring A are, for example, a protected or unprotected hydroxy group; a lower alkoxy group which may optionally be substituted by a group selected from a lower alkylene-dioxyphenyl group, a benzimidazolyl group, a lower alkyl-substituted imidazolyl group, a cyano group, a carboxyl group, a pyridyl group, an N-oxo-pyridyl group, a pyridyl group being substituted by a hydroxy-substituted lower alkyl group, a pyrrolidinyl group, an isoquinolyl group, a pyrimidinyl group, a pyrazinyl group, a quinazolyl group, a phthalazinyl group, a lower

alkoxycarbonyl-substituted piperidyl group, a piperidyl group, a quinolyl group, a tetrazolyl group, a thienyl group, a furyl group, a pyrrolyl group being substituted by a lower alkyl group and a lower alkoxycarbonyl group, a mono- or di-lower alkyl amino group, a lower alkoxy-substituted lower alkoxy group, a lower alkoxy group, a hydroxy group, a carbamoyl group, a lower alkoxy-carbonyl group, a cyclo-lower alkyl group, a hydroxy-lower alkyl group-substituted phenyl group, a carboxy-substituted phenyl group, a lower alkoxy-carbonyl group-substituted phenyl group, a benzoyl group, a mono- or di-lower alkoxy-substituted phenyl group, a nitro-substituted phenyl group, a naphthyl group, a mono- or di-halogenophenyl group, a carbamoyl-substituted phenyl group, a sulfamoyl-substituted phenyl group, a phenyl group being substituted by one or two protected or unprotected amino groups, a biphenylyl group, a phenyl group being substituted by a halogen atom and a nitro group, a di-lower alkylamino-substituted phenyl group, and a lower alkyl-substituted phenyl group; a lower alkylenedioxy group; a halogen atom; a lower alkyl group; a cyclo-lower alkoxy group; a pyridyloxy group; a lower alkenyloxy group; a morpholinocarbonyloxy group; a lower alkyl-substituted piperazinylcarbonyl-oxy group; a pyrrolylcarbonyloxy group being substituted by a lower alkyl group and a nitro group; a pyrrolylcarbonyloxy group; a mono- or di-lower alkylcarbamoyloxy group; a lower alkyl-substituted phenylsulfonyloxy group; and a benzoyloxy group.

When R^1 of the present compounds (I) is a substituted or unsubstituted aryl group, the aryl group is, for example, a 6- to 14-membered partially saturated or unsaturated monocyclic, bicyclic or tricyclic aryl group. The monocyclic aryl group is, for example, a phenyl group, a cyclohexadienyl group, a cyclohexenyl

group, etc. The bicyclic aryl group is, for example, a naphthyl group, an indenyl group, an indanyl group, an azulenyl group, etc. The tricyclic aryl group is, for example, a fluorenyl group, a phenanthrenyl group, an anthracenyl group, etc.

When R^1 of the present compounds (I) is a substituted or unsubstituted heterocyclic group, the heterocyclic group is, for example, a 5- to 12-membered partially saturated or unsaturated heteromonocyclic or heterobicyclic group, such as a 5- to 12-membered partially saturated or unsaturated aromatic heteromonocyclic or heterobicyclic group, or a 5- to 12-membered aliphatic heteromonocyclic or heterobicyclic group.

The 5- to 12-membered aromatic heteromonocyclic or heterobicyclic group is preferably a 5- to 10-membered aromatic heteromonocyclic or heterobicyclic group having 1 to 4 heteroatoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, for example, a pyranyl group, an indazolyl group, a benzotriazolyl group, a pyrrolyl group, an imidazolyl group, a furyl group, a thienyl group, a thiazolyl group, an isoxazolyl group, an oxazolyl group, an oxazolinyl group, a pyrazolyl group, a phthalazinyl group, a quinazolinyl group, a thienopyrimidinyl group, a pyridyl group, a pyrimidinyl group, a pyridazinyl group, a pyrazinyl group, a triazinyl group, a tetrazolyl group, a quinolyl group, an isoquinolyl group, a quinoxalinyl group, an indolyl group, a benzothienyl group, a benzothiazolyl group, a benzoxazolyl group, or a benzimidazolyl group, and a partially saturated group of these groups.

The 5- to 12-membered aliphatic heteromonocyclic or heterobicyclic group is preferably a 5- to 10-membered aliphatic heteromonocyclic group having 1 to 4 heteroatoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, for example, a piperazinyl group, a pyrrolidinyl group, a piperidyl

group, a pyrazolidinyl group, a quinuclidinyl group, a thiomorpholino group, a morpholino group, a hexahydropyrimidinyl group, a tetrahydrofuranyl group, a tetrahydropyranyl group, and a dioxanyl group.

The substituent of the lower alkyl group for R^1 of the present compounds (I) is, for example, a piperidyl group, a pyridyl group, an imidazolyl group, a lower alkyl-substituted piperidyl group, a furyl group, a morpholino group, a tetrahydrofuryl group, a dihydropyridyl group being substituted by a lower alkyl group and an oxo group, a piperazinyl group, a lower alkoxy-carbonyl-substituted piperazinyl group, a cyclo-lower alkyl group, a phenyl group, a lower alkylenedioxyphenyl group, a lower alkoxycarbonyl group, a hydroxy group, a hydroxy-substituted lower alkoxy group, a carboxyl group, a lower alkoxy group, a protected or unprotected amino group, a carbamoyl group, a di-lower alkylamino group, and a pyridylcarbonyloxy group.

The lower alkyl group for R^1 may optionally have 1 to 3 substituents being the same or different, which are selected from the above groups.

The substituent of the cyclo-lower alkyl group for R^1 of the present compounds (I) is, for example, a lower alkoxycarbonyl group, a hydroxy group, a carboxyl group, a lower alkyl group, a lower alkoxy group, a hydroxy-substituted lower alkyl group, or a protected or unprotected amino group.

The cyclo-lower alkyl group for R^1 may optionally have 1 to 3 substituents being the same or different, which are selected from the above groups.

The substituent of the aryl group for R^1 of the present compounds (I) is, for example, a halogen atom, a mono- or di-lower alkylamino group, a

morpholino group, a lower alkyl-substituted pyrimidinyl group, a lower alkyl-substituted pyrazolyl group, a hydroxy-substituted lower alkyl group, a protected or unprotected amino group, a lower alkanoyl-substituted amino group, a lower alkoxy group, a lower alkyl group, a protected or unprotected hydroxy group, a carboxy-substituted lower alkyl group, a lower alkoxy-carbonyl-substituted lower alkyl group, a lower alkoxycarbonyl-substituted lower alkoxy group, a carbamoyl group, a carboxyl group, a lower alkylthio group, a lower alkoxycarbonyl group, a nitro group, a trihalogeno-lower alkyl group, a morpholinocarbonyl group, a carboxy-substituted lower alkoxy group, a di-(lower alkylsulfonyl)amino group, a morpholino-lower alkylcarbamoyl-substituted lower alkoxy group, a sulfamoyl group, a lower alkyl group being substituted by a protected or unprotected amino group, an amino group being substituted by a lower alkyl group and a protecting group for amino group, a lower alkylenedioxy group, a carbamoyl group being substituted by a protected or unprotected amino group, a lower alkylsulfinyl group, and a lower alkyl-sulfonyl group.

The aryl group for R^1 may optionally have 1 to 4 substituents being the same or different, which are selected from the above groups.

The substituent of the heterocyclic group for R^1 of the present compounds (I) is, for example, a hydroxy group, a halogen atom, a lower alkyl group, a phenyl-substituted lower alkyl group, a hydroxy-substituted lower alkyl group, an oxo group, a lower alkoxy group, a protected or unprotected amino group, a mono- or di-lower alkylamino group, a phenyl-lower alkoxy-carbonyl group, a lower alkoxycarbonyl group, a carboxyl group, and a

carbamoyl group.

The heterocyclic group for R^1 may optionally have 1 to 4 substituents being the same or different, which are selected from the above groups.

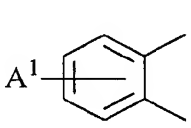
The substituent of the amino group optionally having 1 or 2 substituents for R^1 of the present compounds (I) is, for example, a protecting group for amino group, a pyridyl group, a lower alkanoyl group, a lower alkyl group, a hydroxy-substituted lower alkyl group, a phenyl group, a lower alkanoyloxy-substituted lower alkyl group, and a trihalogeno-lower alkanoyl group, which are the same or different.

When the present compounds (I) have a protected amino group, the protecting group for amino group is, for example, a substituted or unsubstituted lower alkoxycarbonyl group, a lower alkanoyl group, etc., such as a benzyloxy-carbonyl group, a 4-methoxybenzyloxycarbonyl group, a 9-fluorenylmethyloxy-carbonyl group, a tert-butoxycarbonyl group, a 2,2,2-trichloroethyloxycarbonyl group, a formyl group, an acetyl group, a propionyl group, and a butyryl group. Among these groups, the preferable one is an aryl-substituted lower alkoxy-carbonyl group and an unsubstituted lower alkoxycarbonyl group, for example, a benzyloxycarbonyl and a tert-butoxycarbonyl group.

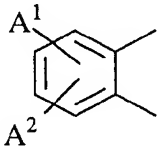
When the present compounds (I) have a protected hydroxy group, the protecting group for hydroxy group is a conventional protecting group such as a substituted or unsubstituted aryl-lower alkyl group, and an acyl group. Among these groups, the preferable one is, for example, an unsubstituted aryl-lower alkyl group (e.g., benzyl, phenethyl), and an acyl group (e.g., formyl, acetyl, propionyl, malonyl, acryloyl, benzoyl).

Among the desired compounds (I) of the present invention, the preferable compounds are compounds of the formula (I) wherein the aryl group is a phenyl group, an indanyl group or a naphthyl group, the heterocyclic group is a piperazinyl group, a pyranyl group, a morpholino group, an indazolyl group, a pyrrolidinyl group, an indolyl group, a benzotriazolyl group, a pyrazinyl group, a pyridyl group, a thiomorpholino group, a pyrrolyl group, a quinolyl group, an isoquinolyl group, a phthalazinyl group, an isoxazolyl group, or a piperidyl group, and the nitrogen-containing aliphatic heterocyclic group is a piperazinyl group or a morpholino group.

The more preferable compounds of the present invention are compounds of the formula (I) wherein Ring A is a benzene ring of the formula:

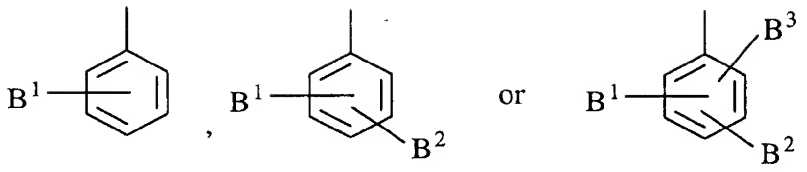


or



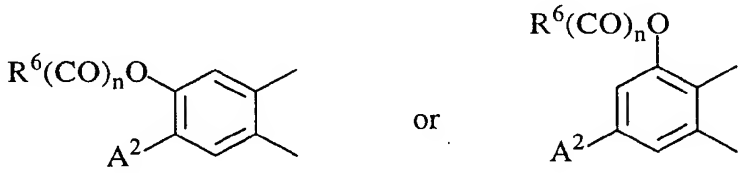
(A^1 and A^2 are the same or different and each a member selected from a protected hydroxy group; a lower alkoxy group; a pridyl-lower alkoxy group; a hydroxy-lower alkyl group-substituted pyridyl-lower alkoxy group; an N-oxopyridyl-lower alkoxy group; a pyrazinyl-lower alkoxy group; a quinolyl-lower alkoxy group; a lower alkoxy group being substituted by an amino-substituted phenyl group; a lower alkoxy group being substituted by a mono- or di-lower alkylamino-substituted phenyl group; a lower alkoxy group being substituted by a lower alkoxy-substituted phenyl group; a lower alkoxy group being substituted by a hydroxy-lower alkyl group-substituted phenyl group; a lower alkoxy group being substituted by a carboxy-substituted phenyl group; and an isoquinolyl-lower alkoxy group), and Ring B is a benzene ring of the

formula:

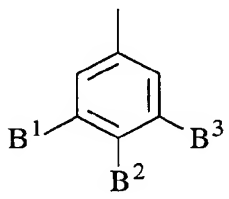


(B1, B2 and B3 are the same or different and each a member selected from a halogen atom, a lower alkyl group, and a lower alkoxy group), and R1 is a phenyl group optionally being substituted by a protected or unprotected amino group, or a pyridyl group optionally being substituted by a protected or unprotected amino group, or a morpholino group, and R2 is a lower alkoxy-carbonyl group or a phenyl-lower alkoxycarbonyl group.

Among the desired compounds (I) of the present invention, more preferable compounds are compounds of the formula (I) wherein Ring A is a benzene ring of the formula:



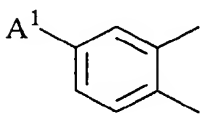
and Ring B is a benzene ring of the formula:



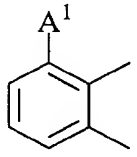
(R6 is (1) a lower alkyl group which may optionally be substituted by a group selected from a pyrrolyl group optionally being substituted by a lower alkyl

group or a lower alkoxycarbonyl group; a pyridyl group optionally being substituted by a hydroxy-lower alkyl group; a thienyl group; an N-oxopyridyl group; a pyrazinyl group; a phenyl group optionally being substituted by 1 to 3 groups being the same or different, and selected from a carboxyl group, a lower alkoxycarbonyl group, a nitro group, an amino group, a mono- or di-lower alkylamino group, a phenyl group, a halogen atom, a lower alkoxy group, a hydroxy-substituted lower alkyl group and a lower alkyl group; a naphthyl group; a quinolyl group; an isoquinolyl group; a benzimidazolyl group; and a cyclo-lower alkyl group, or (2) a pyrrolyl group optionally being substituted by a group selected from a lower alkyl group and a nitro group, A^2 is a hydrogen atom or a lower alkoxy group, B^1, B^2 and B^3 are the same or different and each a halogen atom, a lower alkyl group, or a lower alkoxy group, and n is 0 or 1), and R^1 is a phenyl group, a phenyl group being substituted by a protected or unprotected amino group, or a morpholino group.

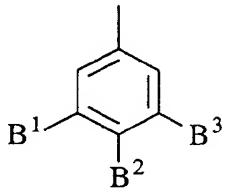
Other preferable compounds of the present invention are compounds of the formula (I) wherein Ring A is a benzene ring of the formula:



or



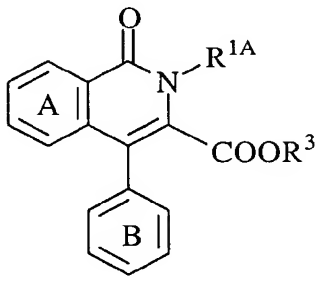
, and Ring B is a benzene ring of the formula:



(A^1 is a protected or unprotected hydroxy group, or a lower alkoxy group being substituted by a group selected from a pyridyl group, a hydroxy-lower alkyl group-substituted pyridyl group, an N-oxopyridyl group,

a pyrazinyl group, an amino-substituted phenyl group, a mono- or di-lower alkyl-amino-substituted phenyl group, a lower alkoxy-substituted phenyl group, a hydroxy-lower alkyl group-substituted phenyl group, an isoquinolyl group and a quinolyl group, B^1, B^2 and B^3 are the same or different and each a halogen atom, a lower alkyl group and a lower alkoxy group), and R^1 is a phenyl group being substituted by a protected or unprotected amino group.

Among the desired compounds (I) of the present invention, pharmaceutically preferable compounds are compounds of the formula (I-A):



(I-A)

wherein Ring A and Ring B are the same or different and each a substituted or unsubstituted benzene ring, R^{1A} is a substituted or unsubstituted aryl group or a substituted or unsubstituted heterocyclic group, and R^3 is a hydrogen atom or an ester residue, or a pharmaceutically acceptable salt thereof.

Examples of the above compounds are compounds of the formula (I-A) wherein Ring A and Ring B are the same or different and each a benzene ring having optionally 1 to 4 substituents selected from

(i) a hydroxy group;

(ii) a halogen atom;

(iii) a lower alkyl group;

(iv) a cyclo-lower alkoxy group;

(v) a lower alkylenedioxy group;

(vi) a lower alkoxy group;

(vii) a lower alkoxy group having 1 to 3 substituents selected from a hydroxy group, a benzoyl group, a lower alkoxycarbonyl group, a carboxyl group, a mono- or di-lower alkylamino group, a lower alkoxy-lower alkoxy group, a lower alkoxy group, a phenyl group, a naphthyl group and a phenyl group having 1 to 3 substituents selected from a nitro group, a halogen atom, a phenyl group, a carboxyl group, a lower alkoxycarbonyl group, a lower alkyl group, a lower alkoxy group, an amino group, a mono- or di-lower alkylamino group and a hydroxy-lower alkyl group; and

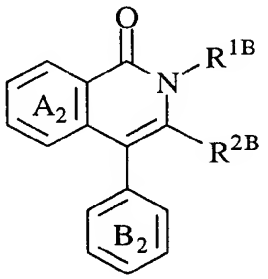
(viii) a lower alkoxy group being substituted by a 5- to 10-membered heterocyclic group having 1 to 4 heteroatoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally 1 to 3 substituents selected from a carboxyl group, a lower alkoxycarbonyl group, a lower alkyl group, a hydroxy-substituted lower alkyl group, a nitro group and an oxo group,

R^{1A} is a phenyl group; a phenyl group having 1 to 4 substituents selected from a protected or unprotected amino group, a halogen atom, a mono- or di-lower alkylamino group, a morpholino group, a lower alkyl-substituted pyrimidinyl group, a lower alkyl-substituted pyrazolyl group, a hydroxy-substituted lower alkyl group, a lower alkanoyl-substituted amino group, a lower alkoxy group, a lower alkyl group, a protected or unprotected hydroxy group, a carboxyl-substituted lower alkyl group, a lower alkoxycarbonyl-substituted lower alkyl group, a lower alkoxycarbonyl-substituted lower alkoxy group, a carbamoyl group, a carboxyl group, a lower alkylthio group, a lower alkoxycarbonyl group, a nitro group, a trihalogeno-lower alkyl group, a morpholinocarbonyl

group, a carboxyl-substituted lower alkoxy group, a di-lower alkylsulfonyl-substituted amino group, a morpholino-lower alkylcarbamoyl-substituted lower alkoxy group, an amino group being substituted by a lower alkyl group and a protecting group for amino group, a lower alkylenedioxy group, a carbamoyl group being substituted by a protected or unprotected amino group, a lower alkylsulfinyl group and a lower alkylsulfonyl group; or a 5- to 10-membered heterocyclic group having 1 to 4 heteroatoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, said heterocyclic group having 1 to 4 substituents selected from a hydroxy group, a halogen atom, a lower alkyl group, a phenyl-substituted lower alkyl group, a hydroxy-substituted lower alkyl group, an oxo group, a lower alkoxy group, a protected or unprotected amino group, a mono- or di-lower alkylamino group, a phenyl-substituted lower alkoxycarbonyl group, a lower alkoxycarbonyl group, a carboxyl group and a carbamoyl group, and

R^3 is a hydrogen atom or a lower alkyl group.

Another embodiment of the compounds of the present invention is an isoquinolinone derivative of the formula (I-B):



(I-B)

wherein Ring A_2 and Ring B_2 are the same or different and each a benzene ring which may optionally be substituted by 1 to 4 groups selected from the group

consisting of a protected or unprotected hydroxyl group; a lower alkylenedioxy group; a halogen atom; a lower alkyl group; a mono- or di-lower alkylcarbamoyloxy group; and a group of the formula: R^{6B}–$(CO)_n$–O

in which R^{6B} is

(i) a lower alkyl group which may optionally have 1 or 2 substituents selected from the group consisting of a 5- to 12-membered heteromonocyclic or heterobicyclic group having optionally 1 to 4 substituents selected from the group consisting of a hydroxy-substituted lower alkyl group, a lower alkyl group, an oxo group and a lower alkoxycarbonyl group; a phenyl or naphthyl group having optionally 1 to 4 substituents selected from the group consisting of a protected or unprotected amino group, a lower alkylenedioxy group, a carboxyl group, a lower alkoxycarbonyl group, a lower alkoxy group, a sulfamoyl group, a carbamoyl group, a nitro group, a phenyl group, a halogen atom, a mono-lower alkylamino group, a di-lower alkylamino group, a lower alkylpiperazinocarbonyl group, a hydroxy-substituted lower alkyl group and a lower alkyl group; a cyano group; a carboxyl group; a mono- or di-lower alkylamino group; a lower alkoxy-substituted lower alkoxy group; a lower alkoxy group; a hydroxy group; a carbamoyl group; a lower alkoxycarbonyl group; a cyclo-lower alkyl group; and a benzoyl group,

(ii) a 5- to 12-membered heteromonocyclic or heterobicyclic group having optionally 1 to 4 substituents selected from the group consisting of a lower alkyl group, a cyano group, a carboxyl group, a mono- or di-lower alkylamino group, a lower alkoxy-substituted lower alkyl group, a hydroxy group, a lower alkoxy group, a carbamoyl group, a lower alkoxycarbonyl group

and a nitro group,

(iii) a cyclo-lower alkyl group,

(iv) a lower alkenyl group, or

(v) a lower alkyl-substituted or unsubstituted phenylsulfonyl group,

n is an integer of 0 or 1,

R^{1B} is

(i) a hydrogen atom,

(ii) a lower alkyl group having optionally 1 to 3 substituents selected from the group consisting of a piperidyl group, a pyridyl group, an imidazolyl group, a lower alkyl-substituted piperidyl group, a furyl group, a morpholino group, a tetrahydrofuryl group, a dihydropyridyl group being substituted by a lower alkyl group and an oxo group, a piperazinyl group, a lower alkoxy-carbonyl substituted-piperazinyl group, a cyclo-lower alkyl group, a phenyl group, a lower alkylenedioxy-phenyl group, a lower alkoxycarbonyl group, a hydroxyl group, a hydroxy-substituted lower alkoxy group, a carboxyl group, a lower alkoxy group, a protected or unprotected amino group, a carbamoyl group, a di-lower alkylamino group and a pyridylcarbonyloxy group,

(iii) a cyclo-lower alkyl group having optionally 1 to 3 substituents selected from the group consisting of a lower alkoxycarbonyl group, a hydroxy group, a carboxyl group, a lower alkyl group, a lower alkoxy group, a hydroxy-substituted lower alkoxy group and a protected or unprotected amino group,

(iv) an unsaturated or partially saturated 6- to 14-membered monocyclic, bicyclic or tricyclic aryl group having optionally 1 to 4 substituents selected from the group consisting of a halogen atom, a mono- or di-lower alkylamino group, a morpholino group, a lower alkyl-substituted pyrimidinyl group, a lower

alkyl-substituted pyrazolyl group, a hydroxy-substituted lower alkyl group, a protected or unprotected amino group, a lower alkanoyl-substituted amino group, a lower alkoxy group, a lower alkyl group, a protected or unprotected hydroxy group, a carboxy-substituted lower alkyl group, a lower alkoxy-carbonyl-substituted lower alkyl group, a lower alkoxycarbonyl-substituted lower alkoxy group, a carbamoyl group, a carboxyl group, a lower alkylthio group, a lower alkoxycarbonyl group, a nitro group, a trihalogeno-lower alkyl group, a morpholinocarbonyl group, a carboxy-substituted lower alkoxy group, a di-lower alkylsulfonylamino group, a morpholino-lower alkyl carbamoyl-substituted lower alkyl group, a sulfamoyl group, a carbamoyl group being optionally substituted by a protected or unprotected amino group, a lower alkylsulfinyl group and a lower alkylsulfonyl group,

(v) a 5- to 12-membered aromatic or aliphatic heteromonocyclic or heterobicyclic group having 1 to 4 substituents selected from the group consisting of a hydroxy group, a halogen atom, a phenyl-substituted lower alkyl group, a hydroxy-substituted lower alkyl group, an oxo group, a lower alkoxy group, a protected or unprotected amino group, a mono- or di-lower alkylamino group, a phenyl-lower alkoxycarbonyl group, a lower alkoxycarbonyl group, a carboxyl group and a carbamoyl group, or

(vi) an amino group having optionally 1 or 2 substituents selected from the group consisting of a protecting group for amino group, a pyridyl group, a lower alkanoyl group, a lower alkoxy group, a hydroxy-substituted lower alkyl group, a phenyl group, a lower alkanoyloxy-substituted lower alkyl group and a trihalogeno-lower alkanoyl group,

R^{2B} is a group of the formula: $-COOR^{3B}$ or a group of the formula:

$-CON(R^{4B})(R^{5B})$

R^{3B} is a hydrogen atom, a lower alkyl group, a tri-lower alkylsilyl group or a phenyl-lower alkyl group, and

a group of the formula:$-N(R^{4B})(R^{5B})$ is a hydroxy-lower alkyl-substituted piperazinyl group, a morpholino group, a pyrrolidinyl group, an imidazolyl-substituted lower alkylamino group or a mono- or di-lower alkylamino group, provided that when R^{1B} is one of the groups of the above-mentioned (i) or (ii), then at least one of Ring A_2 and Ring B_2 is a benzene ring which is substituted by two or more lower alkoxy groups.

Examples of the pharmaceutically preferable compounds are as follows.

6-methoxy-3-methoxycarbonyl-2-morpholino-7-(4-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

6-methoxy-3-methoxycarbonyl-2-morpholino-7-(3-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

6-methoxy-3-methoxycarbonyl-2-morpholino-7-(2-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

6-methoxy-3-methoxycarbonyl-2-phenyl-4-(3,4,5-trimethoxyphenyl)-7-(4-pyridylmethyloxy)-1(2H)-isoquinolinone;

6-methoxy-3-methoxycarbonyl-2-phenyl-4-(3,4,5-trimethoxyphenyl)-7-(3-pyridylmethyloxy)-1(2H)-isoquinolinone; or

6-methoxy-3-methoxycarbonyl-2-phenyl-4-(3,4,5-trimethoxyphenyl)-7-(2-pyridylmethyloxy)-1(2H)-isoquinolinone.

Among the desired compounds (I) of the present invention, other pharmaceutically preferable compounds are as follows.

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(2-pyridylmethyl-oxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(3-aminobenzyloxy)-6-methoxy-3-methoxy-carbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(4-pyridylmethyl-oxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(2-benzimidazolylmethyloxy)-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(3,5-diaminobenzyloxy)-6-methoxy-3-methoxy-carbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-6-methoxy-3-methoxycarbonyl-7-(2-pyridylmethyloxy)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-6-methoxy-3-methoxycarbonyl-7-(3-pyridylmethyloxy)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-6-methoxy-3-methoxycarbonyl-7-(4-pyridylmethyloxy)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-7-(2-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-7-(3-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-7-(4-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(2,5-dimethoxybenzyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(3,5-dimethoxybenzyloxy)-3-methoxycarbonyl-4-

(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-3-methoxycarbonyl-7-(2-pyridylmethyloxy)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-3-methoxycarbonyl-7-(3-pyridylmethyloxy)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-3-methoxycarbonyl-7-(4-pyridylmethyloxy)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(3-aminobenzyloxy)-4-(4-bromo-3,5-dimethoxyphenyl)-3-methoxycarbonyl-1(2H)-isoquinolinone;

2-(4-aminophenyl)-4-(4-chloro-3,5-dimethoxyphenyl)-3-methoxycarbonyl-7-(2-pyridylmethyloxy)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-4-(4-chloro-3,5-dimethoxyphenyl)-3-methoxycarbonyl-7-(3-pyridylmethyloxy)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(3-dimethylaminobenzyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-7-pyrazinylmethyloxy-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-4-(4-chloro-3,5-dimethoxyphenyl)-3-methoxycarbonyl-7-(4-pyridylmethyloxy)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(3,5-diaminobenzyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(6-hydroxymethyl-2-pyridylmethyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(4-carboxybenzyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(3-carboxybenzyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-7-[4-(4-methylpiperazinyl-carbonyl)benzyloxy]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-7-[3-(4-methylpiperazinyl-carbonyl)benzyloxy]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-7-[3-(methylamino)benzyloxy]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(2-hydroxymethylbenzyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-7-(N-oxo-2-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-8-(2-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-8-(3-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-8-(4-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-4-(4-chloro-3,5-dimethoxyphenyl)-7-(6-hydroxy-methyl-2-pyridylmethyloxy)-3-methoxycarbonyl-1(2H)-isoquinolinone;

2-(4-aminophenyl)-4-(4-chloro-3,5-dimethoxyphenyl)-3-methoxy-carbonyl-7-pyrazinylmethyloxy)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methyl-phenyl)-7-(4-pyridylmethyloxy)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methyl-

phenyl)-7-(3-pyridylmethyloxy)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methyl-phenyl)-7-(2-pyridylmethyloxy)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(3,5-diaminobenzyloxy)-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(6-hydroxymethyl-2-pyridylmethyloxy)-3-methoxy-carbonyl-4-(3,5-dimethoxy-4-methylphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(3-methylaminobenzyloxy)-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(2-hydroxymethylaminobenzyloxy)-3-methoxy-carbonyl-4-(3,5-dimethoxy-4-methylphenyl)-1(2H)-isoquinolinone; or

2-(4-aminophenyl)-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methyl-phenyl)-7-(2-pyrazinylmethyloxy)-1(2H)-isoquinolinone.

When the desired compound (I) of the present invention has an asymmetric carbon atom at the substituents of Ring A and Ring B and/or at R^1, it may exist in the form of an optically active isomer thereof owing to said asymmetric carbon atom thereof, and the present invention also includes these optical isomers and a mixture thereof.

The present compounds (I) can clinically be used either in the free form or in the form of a pharmaceutically acceptable salt thereof. The pharmaceutically acceptable salt includes a salt with an inorganic acid such as hydrochloride, sulfate or hydrobromide, or a salt with an organic acid such as acetate, fumarate, oxalate, citrate, methanesulfonate, tosylate, or maleate. The compounds (I) having a substituent such as a carboxyl group may clinically be used in the form of a salt with a base such as an alkali metal salt (e.g., sodium salt, potassium salt)

or an alkaline earth metal salt (e.g., calcium salt) as well.

The desired compound (I) or a salt thereof includes either intramolecular salt or an additive thereof, and solvates or hydrates thereof.

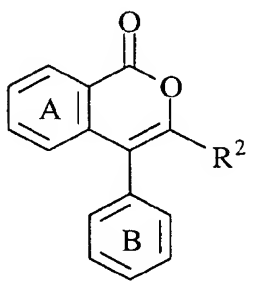
The present compound (I) or a pharmaceutically acceptable salt thereof can be administered either orally or parenterally, and can be formulated into a conventional pharmaceutical preparation such as tablets, granules, capsules, powders, injections, and inhalants.

The dose of the compounds (I) of the present invention or a pharmaceutically acceptable salt thereof may vary in accordance with, for example, the administration routes, and the ages, weights and conditions of the patients. For example, when administered in an injection preparation, it is usually in the range of about 0.0001-0.5 mg/kg/day, preferably in the range of about 0.0005-0.1 mg/kg/day. When administered in an oral preparation, it is usually in the range of about 0.001-30 mg/kg/day, preferably in the range of about 0.05-10 mg/kg/day.

The desired compounds (I) of the present invention may be prepared by the following Processes A, B, and C.

Process A

The desired compounds (I) of the present invention can be prepared by reacting an isocoumarin derivative of the formula (II):



(II)

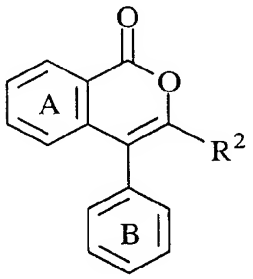
wherein the symbols are the same as defined above, or a salt thereof, with an amine compound of the formula (III):

$$R^1\text{–}NH_2 \qquad \text{(III)}$$

wherein the symbol is the same as defined above, or a salt thereof.

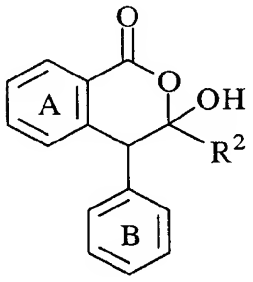
Process B

The desired compounds (I) of the present invention can be prepared by subjecting an isocoumarin derivative of the formula (II) :



(II)

wherein the symbols are the same as defined above, or a salt thereof, to hydrolysis to give a compound of the formula (IV):

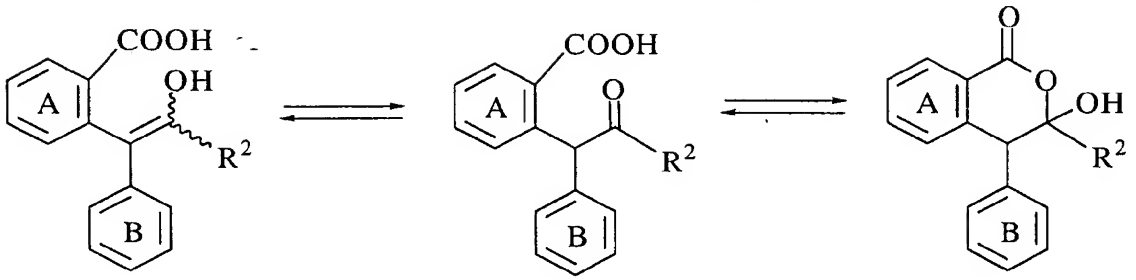


(IV)

wherein the symbols are the same as defined above, and reacting the compound (IV) with an amine compound of the formula (III):

$$R^1\text{–}NH_2 \qquad \text{(III)}$$

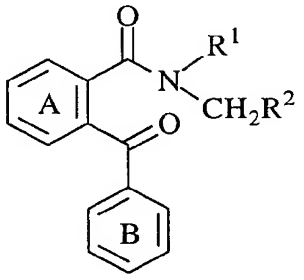
wherein the symbol is the same as defined above, or a salt thereof. The compound of the formula (IV) may exist in a solution in equilibration as follows.



(IV)

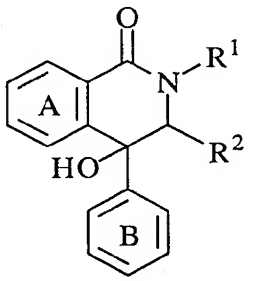
Process C

The desired compounds (I) of the present invention can be prepared by subjecting a benzoylbenzamide compound of the formula (V):



(V)

wherein the symbols are the same as defined above, or a salt thereof, to intramolecular cyclization reaction, to give a compound of the formula (VI):



(VI)

wherein the symbols are the same as defined above, and subjecting the compound (VI) to dehydration reaction.

The compound (I) obtained by Process A, B or C may, if necessary, be converted into a pharmaceutically acceptable salt thereof.

The above Processes A, B and C can be carried out as follows.

Process A

The reaction between the isocoumarin derivative (II) and the amine compound (III) or a salt thereof is carried out in a solvent or without a solvent. The solvent includes, for example, 1,3-dimethyl-2-imidazolidinone (DMI), dimethylformamide, dimethylsulfoxide, ethylene glycol, N-methylpyrrolidone, xylene, dichloroethane, etc. The reaction is carried out at 20 - 150°C, preferably at 40 - 130°C.

Process B

The hydrolysis of the isocoumarin derivative (II) is carried out in the presence of a strong base in a solvent. The strong base includes, for example, an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, lithium hydroxide, etc.), an alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), etc. The solvent includes, for example, water, or a mixture of water and methanol, ethanol, tetrahydrofuran, dioxane, dimethylformamide, etc. The reaction is carried out at 0 - 80°C, preferably at 5 - 60°C.

The reaction between the compound (IV) and the amine compound (III) is carried out in the presence or absence of an acid acceptor in a suitable solvent or without a solvent. The acid acceptor includes N-methylmorpholine, triethylamine, pyridine, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, etc. The solvent may be any solvents used in the above Process A which does not disturb the reaction. The reaction is carried out at 20 - 140°C, preferably at 30 - 100°C.

Process C

The intramolecular cyclization reaction of the benzoylbenzamide

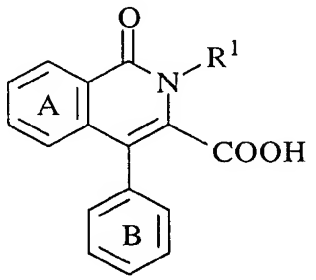
compound (V) is carried out in the presence or absence of a base in a solvent. The base includes, for example, an organic base (e.g., 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), etc.), or an organic base (e.g., sodium methoxide, potassium tert-butoxide, sodium hydride, n-butyl lithium, lithium diisopropyl amide, etc.), and these bases are usually used in an amount of 0.5-5 equivalents, preferably in an amount of 1-2 equivalents, to 1 equivalent of the compound (V). The solvent includes tetrahydrofuran, dimethylformamide, dioxane, dimethoxyethane, benzene, toluene, pyridine, etc., but may be any solvent used in the above Process A which does not disturb the reaction. The reaction is carried out at –50 - 100°C, preferably at –20 - 80°C.

The dehydration reaction of the compound (VI) is carried out in the presence of an acidic catalyst in a solvent. The acidic catalyst includes a sulfonic acid compound (e.g., p-toluenesulfonic acid, methanesulfonic acid, etc.), a carboxylic acid compound (e.g., acetic acid, trifluoroacetic acid, etc.), an inorganic acid compound (e.g., hydrogen chloride, hydrogen bromide, sulfuric acid, etc.), and a Lewis acid (e.g., boron trifluoride ethyl ether, aluminum chloride, etc.), and these acidic catalysts are usually used in an amount of 0.1-5 equivalent, preferably in an amount of 0.2-2 equivalents, to the amount of the compound (VI). The solvent includes, for example, chloroform, dioxane, benzene, toluene, methylene chloride, etc., but may be any solvent used in the above Process A which does not disturb the reaction. The reaction is carried out at 0 - 150°C, preferably at 20 - 110°C.

When R^1 of the amine compound (III) used in the above Processes A and B is an amino group, or a group containing an amino group, these Processes A and B are preferably carried out after introducing a protecting group such as a

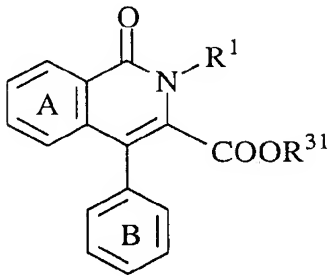
substituted or unsubstituted lower alkoxycarbonyl group (e.g., tert-butoxy-carbonyl group, benzyloxycarbonyl group, etc.), and a lower alkanoyl group (e.g., formyl group, acetyl group, propionyl group, etc.) into said amino group.

The compound of the formula (I) obtained in the above Processes A, B and C wherein the group $-COOR^3$ is a carboxyl group, i.e., a compound of the formula (I-a):



(I-a)

wherein the symbols are the same as defined above, is converted into a compound of the formula (I-b):



(I-b)

wherein R^{31} is an ester residue and the other symbols are the same as defined above, by esterification reaction in a conventional manner. For example, the compound (I-b) is prepared by reacting the compound (I-a) with an esterifying agent in the presence or absence of an acid acceptor in a solvent. The acid acceptor includes, for example, an inorganic base (e.g., an alkali metal hydroxide, an alkali metal carbonate, etc.), and an organic base (e.g., N-methylmorpholine,

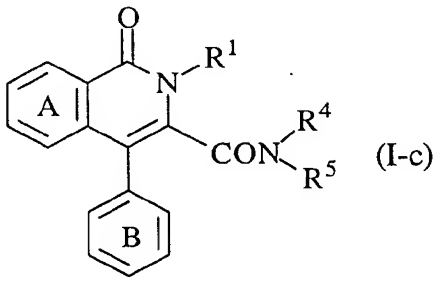
triethylamine, pyridine, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), etc.). The esterifying agent includes, for example, a diazoalkane (e.g., diazomethane, diazoethane, etc.), a dialkyl sulfate (e.g., dimethyl sulfate, diethyl sulfate, etc.), an alkyl halide (e.g., methyl iodide, methyl bromide, ethyl bromide, etc.), a tri-lower alkylsilyldiazoalkane (e.g., trimethylsilyldiazomethane, etc.), an aryl-lower alkyl halide (e.g., benzyl chloride, benzyl bromide, etc.), etc. When a dialkyl sulfate, an alkyl halide or an aryl-lower alkyl halide is used as an esterifying agent, the acid acceptor is usually used in an amount of 1-5 equivalents, preferably in an amount of 1-2 equivalents, to 1 equivalent of the compound (I-a). The reaction is carried out at 0 - 60°C, preferably at 5 - 40°C. When a diazoalkane is used as an esterifying agent, the acid acceptor is usually used in an amount of 1-5 equivalents, preferably in an amount of 1-2 equivalents, to 1 equivalent of the compound (I-a). The reaction is carried out at 0 - 50°C, preferably at 5 - 30°C. The compound of the formula (I-a) wherein the group $-COOR^3$ is a methoxycarbonyl group is prepared under moderate conditions by using trimethylsilyldiazomethane as an esterifying agent in the above reaction. The solvent includes, for example, water, an alcohol (e.g., methanol, ethanol, isopropyl alcohol, etc.), an ether (e.g., diethyl ether, tetrahydrofuran, dioxane, etc.), a ketone (e.g., acetone, methyl ethyl ketone, etc.), as ester (e.g., ethyl acetate, etc.), an aromatic hydrocarbon (e.g., benzene, toluene, etc.), a halogenated hydrocarbon (e.g., methylene chloride, chloroform, etc.), an amide (e.g., N,N-dimethylformamide, N,N-dimethylacetamide, etc.), a sulfoxide (e.g., dimethylsulfoxide, etc.), or a mixture of these solvents.

In addition, the compound (I-b) is prepared by reacting the compound (I-

a) with a lower alcohol (e.g., methanol, ethanol, propanol, butanol, etc.), or an aryl-lower alcohol (e.g., benzyl alcohol, phenethyl alcohol, etc.), under acidic conditions. The acid includes, for example, sulfuric acid, hydrogen chloride, p-toluenesulfonic acid, etc., which is usually used in an amount of 0.01-20 equivalents, preferably in an amount of 0.1-10 equivalents, to 1 equivalent of the compound (I-a). The reaction is preferably carried out in said alcohol with heating under reflux.

When the above-mentioned compound (I-a) has one or more carboxyl group or a mono-substituted or unsubstituted amino group except the 3-carboxyl group (= R^2), said compound (I-a) can be converted into a corresponding compound of the formula (I-a) wherein said carboxyl group is esterified, or said amino group is converted into a mono- or di-lower alkylamino group, by reacting with the above-mentioned esterifying agent.

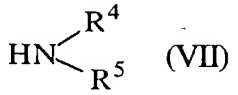
Besides, the compound (I) wherein the substituent R^2 is a group of the formula $-CON(R^4)(R^5)$, i.e., a compound of the formula (I-c):



(I-c)

wherein a group of the formula $-N(R^4)(R^5)$ is a substituted or unsubstituted nitrogen-containing aliphatic heterocyclic group, or a substituted or unsubstituted amino group, and the other symbols are the same as defined above, is prepared by reacting the compound of the formula (I-a) with an amine

compound of the formula (VII):



(VII)

wherein the symbols are the same as defined above, in the presence of an condensing agent, or reacting a reactive derivative (e.g., an acid halide, an active amide, an active ester, a mixed acid anhydride, etc.) of the compound (I-a) with the amide compound (VII) in the presence or absence of a base in a solvent. The base includes an organic base (e.g., pyridine, 4-dimethylaminopyridine, N-methylmorpholine, triethylamine, N,N-dimethylaniline, N,N-diethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene, etc., and an inorganic base (e.g., sodium hydrogen carbonate, potassium hydrogen carbonate, sodium carbonate, etc.). The condensing agent includes, for example, 1,3-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSCI), propanephosphonic anhydride (PPA), etc. The solvent includes, for example, dimethylformamide, methylene chloride, tetrahydrofuran, dioxane, ethyl acetate, and 1,3-dimethyl-2-imidazolidinone, but may be any solvent used in the above Process A which does not disturb the reaction. The reaction is carried out at –20 - 60°C, preferably at 5 - 40°C.

The active ester of the compound (I-a) is preferably an ester of the compound (I-a) with N-hydroxysuccinmide, N-hydroxyphthalimide, 1-hydroxybenzotriazole, or p-nitrophenol.

The acid halide of the compound (I-a) is preferably an acid chloride, an acid bromide, etc.

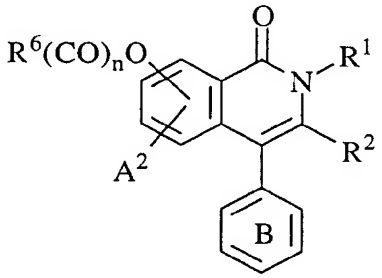
The active amide of the compound (I-a) is preferably an amide of the compound (I-a) with imidazole, etc.

In the preparation of the desired compound (I), the starting compounds (I-a), (I-d), (I-f), (I-h), (II), (III), (IV), (V), (VI) and (VII) in the above Processes A to C as well as to Steps (a) to (d) disclosed hereinafter can be used as well as in the form of a salt thereof. The salt may be, for example, a salt with an alkali metal (e.g., sodium, potassium, lithium, etc.), a salt with an organic base (e.g., pyridine, triethylamine, N-methylmorpholine, etc.), a salt with an inorganic acid (e.g., hydrogen chloride, hydrogen bromide, sulfuric acid, etc.), or a salt with an organic acid (e.g., acetic acid, formic acid, oxalic acid, citric acid, malonic acid. etc.).

The desired compound (I) of the present invention can also be prepared by converting the substituents of Ring A and/or Ring B, or the substituents R^1 and/or R^2 into other substituents. The method for conversion reaction of these substituents is selected in accordance with the kinds of the substituents to be required, and may be the following steps (a) to (t).

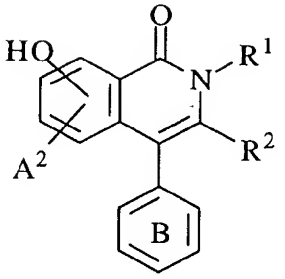
Step (a)

The compound of the formula (I-e):



(I-e)

wherein the symbols are the same as defined above, is prepared by reacting a compound of the formula (I-d):



(I-d)

wherein the symbols are the same as defined above, or a salt thereof, with a compound of the formula (VIII-a):

$$R^6\text{–}COOH \qquad \text{(VIII-a)}$$

wherein R^6 is the same as defined above, or a reactive derivative thereof, or with a compound of the formula (VIII-b):

$$R^6\text{–}X \qquad \text{(VIII-b)}$$

wherein X is a leaving group, and R^6 is the same as defined above.

The leaving group (X) of the compound (VIII-b) is, for example, a hydroxy group, a trifluoromethanesulfonyloxy group, a p-tosyloxy group, a methanesulfonyloxy group, or a halogen atom such as chlorine, bromine, iodine, etc.

The reaction between the compound (I-d) and the compound (VIII-a) is carried out in the presence of a condensing agent (e.g., 1,3-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, diethylphosphonic cyanide, diphenylphosphonic azide, etc.). The reaction between a reactive derivative of the compound (VIII-a) (e.g., an active ester such as N-hydroxysuccinimide ester, N-hydroxyphthalimide ester, 1-hydroxybenzotriazole ester, or an acid halide such as acid chloride, acid bromide, etc.) and the compound (I-d) is carried out in the presence of an acid acceptor such as an

alkali metal hydroxide (e.g., sodium hydrochloride), an alkali metal hydrogen carbonate (e.g., sodium hydrogen carbonate), an alkali metal carbonate (e.g., sodium carbonate), or an organic base (e.g., triethylamine, pyridine, etc.), and if necessary, 4-dimethylaminopyridine (DMAP), etc. may be added to the reaction mixture in a catalytic amount. The reaction is carried out at 0 - 80°C, preferably at 5 - 60°C.

The reaction between the compound (I-d) and the compound (VIII-b) is carried out, for example, according to the method disclosed in Mitsunobu, et al. (cf., Synthesis, pp. 1-28, 1981), when the leaving group X is a hydroxy group. That is, the compound (I-d) and the compound (VIII-b) are reacted in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine in a solvent such as tetrahydrofuran, dioxane, ethyl acetate, dimethylformamide, chloroform, methylene chloride, benzene, toluene, dimethoxyethane, etc. The reaction is carried out at 0 - 60°C, preferably at 5 - 40°C.

When the leaving group X of the compound (VIII-b) is a trifluoromethanesulfonyloxy group, p-tosyloxy group, methanesulfonyloxy group, or a halogen atom such as chlorine, bromine, iodine, etc., the reaction between the compound (I-d) and the compound (VIII-b) is carried out in the presence of a base. The reaction may also be carried out in the presence or absence of a base and/or a copper catalyst. The base includes, for example, an inorganic base such as an alkali metal hydride (e.g., sodium hydride), an alkali metal amide (e.g., sodium amide), an alkali metal alkoxide (e.g., sodium methoxide, potassium tert-butoxide), an alkali metal hydroxide (e.g., sodium hydroxide), an alkali metal carbonate (e.g., sodium carbonate), and an organic base such as N-methylmorpholine, triethylamine, pyridine, etc. The base is usually used in an amount

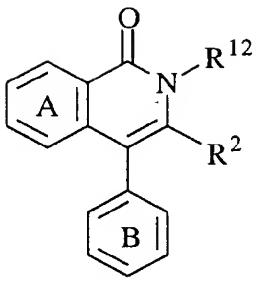
of 1 to 5 equivalents, preferably in an amount of 1 to 2 equivalents, to 1 equivalent of the compound (I-d). When the substituent R^1 is an amino group optionally having one substituent, or a substituent containing an amino group optionally having one substituent, it is preferable to carry out the reaction after introducing a protecting group such as a lower alkoxycarbonyl group (e.g., tert-butoxycarbonyl group), an aryl-lower alkoxycarbonyl group (e.g., benzyloxy-carbonyl group), or a lower alkanoyl group (e.g., formyl group, acetyl group, propionyl group) into said amino group.

The copper catalyst may be copper (I) iodide, copper (II) bromide, copper (0) powder, copper (I) oxide, copper (II) bromide, etc. The reaction is carried out at 10 - 160°C, preferably at 20 - 120°C.

The desired compound (I) wherein Ring A is a benzene ring being substituted by a group selected from a lower alkyl-substituted piperazinyl-carbonyloxy group, and a mono- or di-lower alkylcarbamoyloxy group is prepared by reacting the compound (I-d) with phosgene or triphosgene, followed by reacting the resulting corresponding product (chloroformate compound) with a lower alkyl-substituted piperazine or a mono- or di-lower alkylamine in the presence or absence of a base (e.g., triethylamine, N-methyl-morpholine, pyridine, 4-dimethylaminopyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), etc.). The reaction is carried out at 0 - 80°C, preferably at 10 - 40°C.

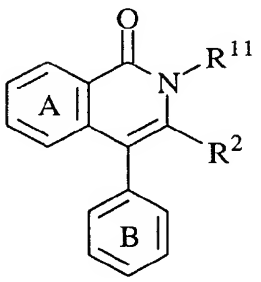
Step (b)

The compound of the formula (I-g):



(I-g)

wherein R^{12} is an amino-substituted lower alkyl group, an amino-substituted cyclo-lower alkyl group, an amino-substituted aryl group, an amino-substituted heterocyclic group, or an amino group, and the other symbols are the same as defined above, is prepared by removing a protecting group for amino group from a compound of the formula (I-f):



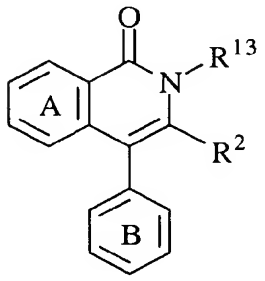
(I-f)

wherein R^{11} is a lower alkyl group being substituted by a protected amino group, a cyclo-lower alkyl group being substituted by a protected amino group, an aryl group being substituted by a protected amino group, a heterocyclic group being substituted by a protected amino group, or a protected amino group, and the other symbols are the same as defined above, or a salt thereof.

The removal of the protecting group is carried out by a conventional method such as acid-treatment, base-treatment, catalytic reduction, etc., which is selected according to the kinds of the protecting group to be removed. The reaction is carried out at 0 - 150°C, preferably at 5 - 110°C.

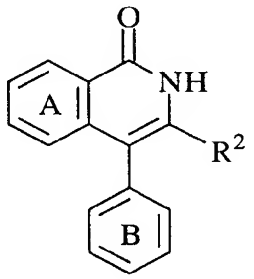
Step (c)

The compound of the formula (I-i):



(I-i)

wherein R^{13} is a substituted or unsubstituted lower alkyl group, and the other symbols are the same as defined above, is prepared by reacting a compound of the formula (I-h):



(I-h)

wherein the symbols are the same as defined above, or a salt thereof, with a compound of the formula (IX):

$$R^{13}\text{–}X^1 \qquad \text{(IX)}$$

wherein X^1 is a halogen atom, and R^{13} is the same as defined above.

The reaction between the compound (I-h) and the compound (IX) is carried out in the presence of an acid acceptor. The acid acceptor is, for example, an alkali metal hydroxide (e.g., sodium hydroxide), an alkali metal hydrogen carbonate (e.g., sodium hydrogen carbonate), an alkali metal carbonate (e.g., sodium carbonate), an alkali metal hydride (e.g., sodium

hydride), or an organic base (e.g., triethylamine, pyridine, 1,8-diazabicyclo[5.4.0]-undec-7-ene, etc.). The reaction is carried out at 0 - 100°C, preferably at 20 - 80°C.

Step (d)

The desired compound (I) wherein the substituent of Ring A and/or the substituent R^1 are a substituent containing an esterified carboxyl group (e.g., a lower alkoxycarbonyl-substituted aryl group, a lower alkoxycarbonyl-substituted-lower alkyl group, a lower alkoxycarbonyl-substituted cyclo-lower alkyl group, a lower alkoxycarbonyl-substituted lower alkyl-substituted aryl group, a lower alkoxycarbonyl-substituted lower alkoxy-substituted aryl group, etc.) is prepared by subjecting a corresponding compound of the formula (I) wherein the substituent of Ring A and/or the substituent R^1 are a substituent containing a free carboxyl group, to esterification reaction. The reaction is carried out in the same manner as in the esterification reaction of the compound (I-a) as mentioned above.

Step (e)

The desired compound (I) wherein the substituent of Ring A and/or the substituent R^1 are a substituent containing a free carboxyl group (e.g., a carboxy-substituted aryl group, a carboxy-substituted cyclo-lower alkyl group, a carboxy-lower alkyl-substituted aryl group, a carboxy-lower alkyl group, a carboxy-lower alkoxy-substituted aryl group, a carboxy-substituted lower alkoxy group, a carboxy-aryl-substituted lower alkyl group, etc.) is prepared by subjecting a corresponding compound of the formula (I) wherein the substituent of Ring A and/or the substituent R^1 are a substituent containing an esterified

carboxyl group, to de-esterification reaction, for example, hydrolysis with a base (e.g., sodium hydroxide), an acid-treatment with a trifluoroacetic acid, hydrogen chloride, hydrogen bromide, etc., or reduction under hydrogen atmosphere with palladium-black, or palladium-carbon, which is selected according to the kinds of the ester residue to be removed. Among these de-esterification reactions, the hydrolysis with a base is carried out at 5 - 70°C, the acid-treatment is carried out at 5 - 80°C, and the reduction is carried out at 10 - 40°C.

Step (f)

The desired compound (I) wherein R^1 is an aryl group being substituted by a protected or unprotected amino-substituted carbamoyl group, or an aryl group being substituted by a morpholinocarbonyl group is prepared by reacting a corresponding compound of the formula (I) wherein R^1 is carboxy-substituted aryl group with an amine compound of the formula:

$$HN(R^a)(R^b)$$

wherein one of R^a and R^b is a hydrogen atom, and the other is a protected or unprotected amino group, or both combine at their termini together with the adjacent nitrogen atom to form a morpholino group, in the presence of a condensing agent. The condensing agent includes a conventional one which is usually used in the amido-bond formation reaction between a carboxylic acid and an amine, for example, 1,1-carbonyldiimidazole (CDI), DCC, WSCI, isobutyl chloroformate and N-methylmorpholine, etc. The reaction is carried out at 0 - 50°C. When R^a or R^b of the product is a protected amino group, if necessary, said protecting group may be removed by a conventional method.

The desired compound (I) wherein the group R^1 is an aryl group being

substituted by a morpholino-lower alkylcarbamoyl-substituted lower alkoxy group is prepared by reacting a corresponding compound of the formula (I) wherein R^1 is an aryl group being substituted by a carboxyl-substituted lower alkoxy group with a morpholino-lower alkylamine in the same manner as above.

The desired compound (I) wherein Ring A is a lower alkoxy-substituted benzene ring being substituted by a carbamoyl group is prepared by reacting a corresponding compound (I) wherein Ring A is a benzene ring being substituted by a carboxyl-substituted lower alkoxy group with ammonia in the same manner as above.

Step (g)

The desired compound (I) wherein the substituent of Ring A and/or the group R^1 is a substituent containing an amino group (e.g., an amino-lower alkyl-substituted aryl group, an amino-substituted aryl-substituted lower alkyl group, etc.) is prepared by removing a lower alkanoyl group or a protecting group for amino group from a corresponding compound of the formula (I) wherein the substituent of Ring A and/or the group R^1 is a substituent containing a mono- or di-lower alkanoylamino group or a protected amino group. The removal of said protecting group for amino group or said lower alkanoyl group is carried out by a conventional method (e.g., acid-treatment, base-treatment, catalytic reduction, etc.). The acid-treatment is carried out at 5 - 120°C, the base-treatment is carried out at 5 - 40°C, and the catalytic reduction is carried out at 10 - 40°C.

Step (h)

The desired compound (I) wherein the substituent of Ring A and/or the

group R^1 is a substituent containing a heterocyclic group (e.g., piperazinyl group, piperidinyl group, or pyrrolidinyl group) is prepared by removing the N-substituent (i.e., a lower alkoxycarbonyl group, or an aryl-lower alkoxycarbonyl group) from a corresponding compound of the formula (I) wherein the substituent of Ring A and/or the group R^1 is a substituent containing a heterocyclic group having a substituent at the N-position selected from a lower alkoxycarbonyl group and an aryl-lower alkoxycarbonyl group (e.g., fluorenyl-lower alkoxycarbonyl group, phenyl-lower alkoxycarbonyl group, etc.). The removal of these groups is carried out by the same method as in the above Step (g).

Step (i)

The desired compound (I) wherein the group R^1 is a mono-lower alkanoylamino group, a di-lower alkanoylamino group or a mono- or di-lower alkanoylamino-substituted aryl group is prepared by reacting a corresponding compound of the formula (I) wherein the group R^1 is an amino group or an aryl group being substituted by an amino group with a lower alkanoic aid or a reactive derivative thereof. The lower alkanoic acid includes, for example, an alkanoic acid having 1 to 6 carbon atoms (e.g., formic acid, acetic acid, propionic acid, etc.). The reactive derivative of alkanoic acid is, for example, an acid halide (e.g., acid chloride, acid bromide, etc.), an acid anhydride, or a mixed acid anhydride. When a free lower alkanoic acid is used, the reaction is carried out in the presence of a condensing agent (e.g., 1,3-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, diethylphosphoric cyanide, diphenylphosphoric azide). When a reactive derivative of the above alkanoic acid is used, the reaction is carried out in the presence of an acid

acceptor such as an organic base (e.g., triethylamine, pyridine, etc.), an alkali metal hydroxide, an alkali metal hydrogen carbonate, an alkali metal carbonate, etc. In the reaction, the conversion from the compound (I) wherein R^1 is an amino group into the corresponding compound (I) wherein R^1 is a mono-lower alkanoylamino group is carried out by controlling the amount of the lower alkanoic aid or a reactive derivative thereof in 0.8-1 equivalent to the amount of the starting compound. The conversion from the compound (I) wherein R^1 is an amino group into the corresponding compound (I) wherein R^1 is a di-lower alkanoylamino group is carried out by controlling the amount of the lower alkanoic aid or a reactive derivative thereof in 2-3 equivalents to the amount of the starting compound. The reaction is carried out at –30 - 80°C, preferably at –20 - 50°C.

Step (j)

The desired compound (I) wherein the group R^1 is an amino group being substituted by one or two groups selected from a lower alkyl group and a hydroxy-substituted lower alkyl group is prepared by reacting a corresponding compound of the formula (I) wherein the group R^1 is a mono-substituted or unsubstituted amino group with an alkylating agent such as a lower alkyl halide (e.g., a lower alkyl chloride, a lower alkyl bromide, a hydroxy-lower alkyl chloride, a hydroxy-lower alkyl bromide, etc.) wherein the alkyl moiety may optionally be substituted by a hydroxy group, or a lower alkyl-lower alkane-sulfonate (e.g., a lower alkyl methanesulfonate, etc.), lower alkyl arylsulfonate (e.g., a lower alkyl p-toluenesulfonate) wherein the alkyl moiety may optionally be substituted by a hydroxy group in the presence or absence of an acid

acceptor. The acid acceptor is, for example, an alkali metal hydroxide (e.g., sodium hydroxide), an alkali metal hydrogen carbonate (e.g., sodium hydrogen carbonate), an alkali metal carbonate (e.g., sodium carbonate), or an organic base (e.g., triethylamine, pyridine, etc.). The desired compound (I) wherein the group R^1 is an amino group being substituted by one group selected from a lower alkyl group and a hydroxy-substituted lower alkyl group is prepared by reacting a corresponding compound of the formula (I) wherein the group R^1 is unsubstituted amino group with a lower alkyl aldehyde wherein the alkyl moiety may optionally be substituted by a hydroxy group, and subjecting the product to reduction. The reducing agent is preferably sodium cyanoborohydride, sodium borohydride, sodium triacetoxyborohydride, formic acid, etc. The solvent may be, for example, water, acetic acid, tetrahydrofuran, dioxane, chloroform, methylene chloride, methanol, ethanol, etc., or a mixture of these solvents. The reaction is carried out at 0 - 70°C, preferably at 5 - 50°C. The compound (I) wherein the group R^1 is an amino group being substituted by a lower alkanoyloxy-lower alkyl group is prepared in the same esterification reaction as in the preparation of the compound [I-b] from the compound [I-a], but preferably prepared by reacting a corresponding compound of the formula (I) wherein the group R^1 is an amino group being substituted by a hydroxy-substituted lower alkyl group with a lower alkanoic acid in the presence of a condensing agent (e.g., 1,3-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, diethyl phosphoric cyanide, diphenylphosphoric azide, etc.), or with a reactive derivative of the above lower alkanoic acid such as an active ester (e.g., N-hydroxysuccinimide ester, N-hydroxy-

phthalimide ester, 1-hydroxybenzotriazol ester, etc.), a corresponding acid halide, a corresponding mixed acid anhydride, in the presence of an acid acceptor such as an alkali metal hydroxide (e.g., sodium hydroxide, etc.), an alkali metal hydrogen carbonate (e.g., sodium hydrogen carbonate, etc.), an alkali metal carbonate (e.g., sodium carbonate, etc.), or an organic base (e.g., triethylamine, pyridine, etc.). The reaction is carried out at –30 - 80°C, preferably at –20 - 50°C.

Step (k)

The desired compound (I) wherein the group R^1 is an aryl group being substituted by a di-(lower alkylsulfonyl) amino group is prepared by reacting a corresponding compound of the formula (I) wherein the group R^1 is an amino-substituted aryl group with a lower alkyl sulfonyl halide (e.g., a lower alkyl sulfonyl chloride, a lower alkyl sulfonyl bromide, etc.) in the presence of the same acid acceptor as those used in the above Step (j), i.e., an organic base (e.g., triethylamine, pyridine, etc.). The reaction is carried out at 0 - 80°C, preferably at 10 - 60°C.

Step (ℓ)

The desired compound (I) wherein the group R^1 is a hydroxy-substituted aryl group, or the desired compound (I) wherein the substituent of Ring A and/or Ring B is a hydroxy group is prepared by removing the protecting groups from a corresponding compound of the formula (I) wherein the group R^1 is a protected hydroxy-substituted aryl group, or a corresponding compound of the formula (I) wherein the substituent of Ring A and/or Ring B is a protected hydroxy group. The removal of the protecting group is carried out by a

conventional method such as acid-treatment, base-treatment, catalytic reduction, etc. which should be selected according to the kinds of the protecting groups to be removed. The reaction is carried out at 0 - 80°C, preferably at 5 - 50°C.

Step (m)

The desired compound (I) wherein the group B^2 of Ring B is a hydroxy group is prepared by treating a corresponding compound of the formula (I) wherein B^2 is a lower alkoxy group by a conventional method, such as acid-treatment. The reaction is carried out at 10 - 150°C, preferably at 20 - 120°C.

Step (n)

The desired compound (I) wherein the group R^1 is an aryl group being substituted by a group selected from a lower alkylsulfinyl group and a lower alkylsulfonyl group is prepared by oxidizing a corresponding compound of the formula (I) wherein R^1 is an aryl group being substituted by a lower alkylthio group. The oxidization reaction is carried out by using an oxidizing agent. The oxidizing agent is, for example, a peroxide compound such as 3-chloro-perbenzoic acid, peracetic acid, hydrogen peroxide, trifluoroperacetic acid, etc., sodium periodate, osmium tetraoxide, sodium bromite, etc. When an oxidizing agent is used in an amount of 0.8-1 equivalent to 1 equivalent of the starting compound, there is obtained the compound of the formula (I) wherein R^1 is an aryl group being substituted by a lower alkylsulfinyl group. When an oxidizing agent is used in an amount of 2-3 equivalents to 1 equivalent of the starting compound, there is obtained the compound of the formula (I) wherein R^1 is an aryl group being substituted by a lower alkylsulfonyl group. The reaction is carried out at –10 - 60°C, preferably at 5 - 40°C.

Step (o)

The desired compound (I) wherein the group R^1 is a heterocyclic group being substituted by one or two oxo groups (e.g., a thiomorpholino group being substituted by one or two oxo groups) is prepared by treating a corresponding compound of the formula (I) wherein R^1 is a heterocyclic group in the same manner as in the above Step (n).

Step (p)

The desired compound (I) wherein the group R^1 is an aryl group being substituted by a mono- or di-lower alkylamino group, or a lower alkyl group being substituted by a mono- or di-lower alkylamino group is prepared in the same manner as in the above Step (j), but is prepared by reacting a corresponding compound of the formula (I) wherein R^1 is an amino-substituted aryl group or an amino-substituted lower alkyl group in the presence or absence of an acid acceptor with a lower alkyl halide (e.g., a lower alkyl chloride, a lower alkyl bromide, etc.). The acid acceptor is, for example, an alkali metal hydroxide, an alkali metal hydrogen carbonate, an alkali metal carbonate, an organic base (e.g., triethylamine, pyridine, etc.). When an alkylating agent is used in an amount of 0.8-1 equivalent to 1 equivalent of the starting compound, there is obtained the compound (I) wherein the group R^1 is an aryl group (or a lower alkyl group) substituted by a mono-lower alkylamino group. When an alkylating agent is used in an amount of 2-3 equivalents to 1 equivalent of the starting compound, there is obtained the compound (I) wherein the group R^1 is an aryl group (or a lower alkyl group) being substituted by a di-lower alkyl-amino group. The reaction is carried out at 0 - 60°C, preferably at 5 - 40°C. The

desired compound (I) wherein the group R^1 is an aryl group being substituted by an amino group being substituted by a lower alkyl group and a protecting group for amino group is prepared by treating a corresponding compound of the formula (I) wherein R^1 is an aryl group substituted by an amino group being substituted by one protecting group for amino group in the same manner as above. Moreover, the compound (I) wherein the group R^1 is a mono-lower alkylamino-substituted aryl group is obtained by removing a protecting group from a corresponding compound of the formula (I) wherein R^1 is an aryl group being substituted by an amino group being substituted by a lower alkyl group and a protecting group for amino group by a conventional method.

Step (q)

The compound (I) wherein the group R^1 is a pyridylcarbonyloxy-lower alkyl group is prepared by reacting a corresponding compound of the formula (I) wherein R^1 is a hydroxy-substituted lower alkyl group with a pyridine-carboxylic acid in the presence of a condensing agent (e.g., 1,3-dicyclohexyl-carbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, diethyl phosphoric cyanide, diphenylphosphoric azide, etc.), or with a reactive derivative of a pyridinecarboxylic acid (e.g., active ester such as N-hydroxy-succinimide ester, N-hydroxyphthalimide ester, 1-hydroxybenzotriazole ester, etc., pyridinecarboxylic halide) in the presence of an acid acceptor such as an alkali metal hydroxide (e.g., sodium hydroxide, etc.), an alkali metal hydrogen carbonate (e.g., sodium hydrogen carbonate, etc.), an alkali metal carbonate (e.g., sodium carbonate, etc.), an alkali metal hydride (e.g., sodium hydride, etc.), or an organic base (e.g., triethylamine, pyridine, etc.). The reaction is carried out

at 0 - 60°C, preferably at 5 - 40°C.

Step (r)

The compound (I) wherein Ring A is a benzene ring being substituted by a tetrazolyl-lower alkoxy group is prepared by reacting a corresponding compound of the formula (I) wherein Ring A is a benzene ring being substituted by a cyano-lower alkoxy group, with a metal azide such as sodium azide, tributyltin azide. The reaction is carried out at 30 - 120°C, preferably at 50 - 100°C.

Step (s)

The compound (I) wherein the substituent of Ring A is a group containing a heterocyclic group substituted by an oxo group (e.g., an oxo-substituted pyridyl-substituted lower alkyl group) is prepared by treating a corresponding compound of the formula (I) wherein the substituent of Ring A is a group containing a heterocyclic group with an oxidizing agent (e.g., 3-chloro-perbenzoic acid, hydrogen peroxide, peracetic acid, etc.). The reaction is carried out in the same manner as in the above Step (n).

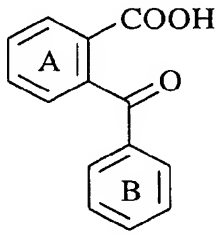
Step (t)

The compound (I) wherein the group R^1 is a heterocyclic group (e.g., piperazinyl group) having a hydroxy-lower alkyl group at the N-position is prepared by reacting a corresponding compound of the formula (I) wherein the group R^1 is a heterocyclic group with a lower alkyl halide (e.g., hydroxy-lower alkyl chloride, hydroxy-lower alkyl bromide, etc.) wherein the alkyl moiety is substituted by a hydroxy group, in the presence or absence of the same acid acceptor (e.g., an alkali metal carbonate such as sodium carbonate) as those

used in the above Step (j). The reaction is carried out at 40 - 120°C, preferably at 50 - 100°C.

The solvent used in the above Steps (a) to (t) may be any one which does not disturb the reaction, for example, dioxane, ethylene glycol dimethyl ether, dimethyl acetamide, dimethylformamide, hexamethylphosphoramide, benzene, tetrahydrofuran, toluene, ethyl acetate, a lower alcohol, methylene chloride, chloroform, carbon tetrachloride, 1,3-dimethyl-2-imidazolidinone, acetic acid, diethyl ether, dimethoxyethane, dimethylsulfoxide, water, or a mixture of these solvents.

The starting compound (II) is prepared, for example, by reacting a benzoylbenzoic acid compound of the formula (i):



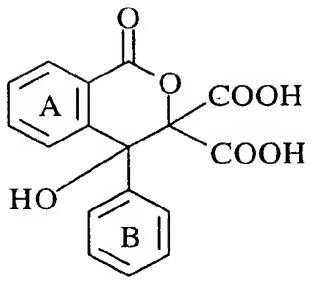
(i)

wherein the symbols are the same as defined above, with a malonic acid compound of the formula (ii):

$$X^2\text{–}CH(COOZ^1)_2 \qquad \text{(ii)}$$

wherein X^2 is a leaving group, and Z^1 is a protecting group for carboxyl group, in the presence of a base,

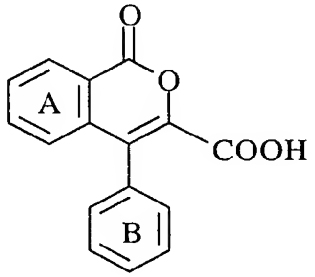
removing the protecting group from the product to give a compound of the formula (iii):



(iii)

wherein the symbols are the same as defined above;

subjecting the compound (iii) to decarboxylation reaction and dehydration reaction in the presence or absence of an acid to give a compound of the formula (iv):

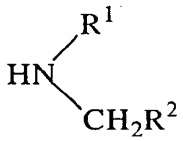


(iv)

wherein the symbols are the same as defined above;

if necessary, followed by converting the 3-carboxyl group of the compound (iv) into the substituent R^2 by esterification or amidation by a conventional method.

The starting compound (V) is prepared, for example, by condensing the compound of the above formula (i) with a compound of the formula (v):

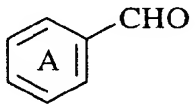


(v)

wherein the symbols are the same as defined above, in the same manner as in the condensation reaction between the compound (I-a) and the amine compound

(VIII).

The benzoyl benzoic acid compound (i) is prepared by a conventional method, for example, by treating a benzaldehyde compound of the formula (vi):

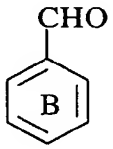


(vi)

wherein Ring A is the same as defined above, with a halogen (bromide, etc.),

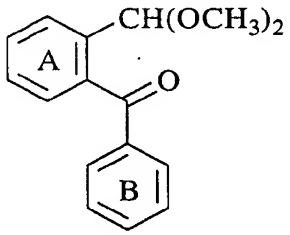
reacting the resulting o-halogeno benzaldehyde compound with an acetalization agent, for example, with a lower alkyl orthoformate (e.g., methyl orthoformate, etc.), in the presence of an acidic catalyst (e.g., a strong acidic resin, etc.) to protect the formyl group,

reacting the product with an aldehyde compound of the formula (vii):



(vii)

wherein Ring B is the same as defined above, oxidizing the product, i.e., treating with an oxidizing agent such as manganese dioxide, etc., to give a compound of the formula (viii):



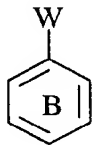
(viii)

wherein the symbols are the same as defined above,

subjecting the compound (viii) to deacetalization by treating with an acid (e.g., hydrochloric acid, trifluoroacetic acid, a strong acidic resin),

followed by treating with an oxidizing agent (e.g., sodium chlorite).

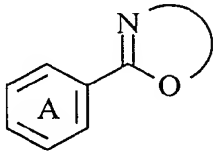
Besides, in the preparation of the compound (i) as mentioned above, a benzoic acid compound of the following formula (ix) is also used instead of the compound (vii).



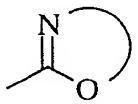
(ix)

wherein W is a di-lower alkyl-substituted carbamoyl group, a lower alkoxy-carbonyl group, or a carboxyl group forming a salt with an alkali metal (e.g., sodium, potassium, etc.), and Ring B is the same as defined above.

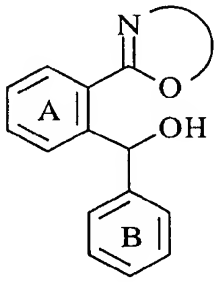
Moreover, the starting compound (i) of the present invention is prepared by reacting a compound of the formula (x):



(x)

wherein a group of the formula: 

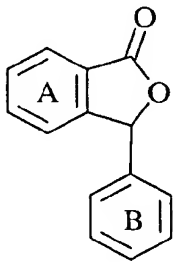
is a heterocyclic group which may optionally be substituted by a lower alkyl group, etc., and Ring A is the same as defined above, with the compound (vii) in the presence of a base (e.g., n-butyl lithium, etc.) to give a compound of the formula (xi):



(xi)

wherein the symbols are the same as defined above;

heating the compound (xi) in the presence of an acid (e.g., an inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, etc.) to give a compound of the formula (xii):



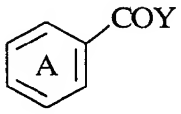
(xii)

wherein the symbols are the same as defined above;

subjecting the compound (vii) to hydrolysis with a base (e.g., an alkali metal hydroxide such as potassium hydroxide, sodium hydroxide, etc.);

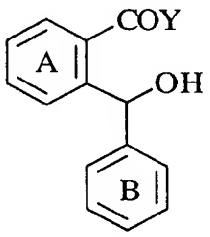
then, followed by subjecting the product to oxidation.

The compound (xii) is prepared by reacting a compound of the formula (xiii):



(xiii)

wherein Y is a mono- or di-lower alkylamino group, and Ring A is the same as defined above, with the compound (vii) in the presence of a base (e.g., sec-butyl lithium, etc.) to give a compound of the formula (xiv):



(xiv)

where the symbols are the same as defined above, followed by heating the

compound (xiv) in the presence of an acid such as an inorganic acid (e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, etc.).

Throughout the present description and the claims, the "alkyl group" means an alkyl group having 1 to 16 carbon atoms, and preferably a straight chain or branched chain alkyl group having 1 to 8 carbon atoms . The "lower alkyl group", the "lower alkoxy group" and the "lower alkylene group" mean ones having 1 to 6 carbon atoms, respectively, and preferably ones having 1 to 4 carbon atoms. The "lower alkenyl group" and the "lower alkynyl group" mean ones having 2 to 7 carbon atoms, respectively, and preferably a straight chain or branched chain one having 2 to 5 carbon atoms. The "lower alkylene-dioxy group" and the "alkanoyl group" mean ones having 1 to 7 carbon atoms, respectively, and preferably a straight chain or branched chain one having 1 to 5 carbon atoms. The "cyclo-lower alkyl group" means cycloalkyl groups having 3 to 8 carbon atoms, preferably ones having 3 to 6 carbon atoms.

BEST MODE FOR CARRYING OUT THE INVENTION

Representatives of the present compound (I) prepared by the above Processes are exemplified in Tables 1-46, but the present invention should not be construed to be limited thereto.

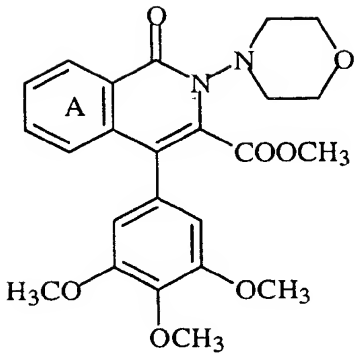
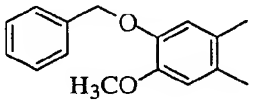
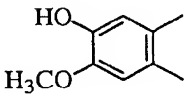
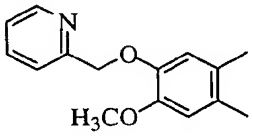


Table 1

Ex. No.	Ring A	Physicochemical properties
1		m.p. 173-174°C
2		m.p. 231-233°C
3*		m.p. 200-203°C (decomp.)

*: monohydrochloride

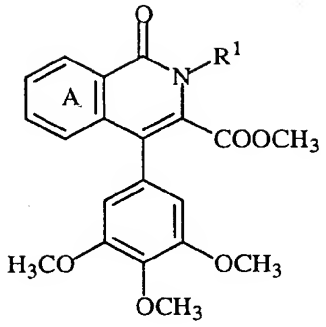
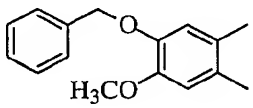
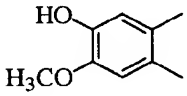
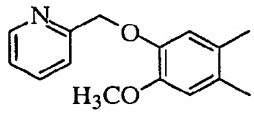
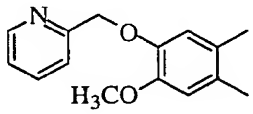
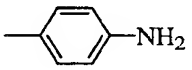
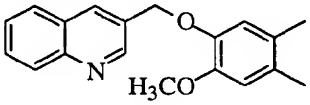
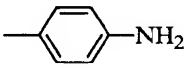
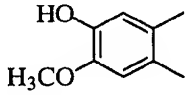
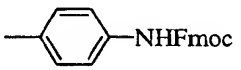
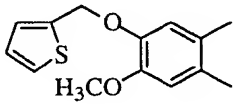
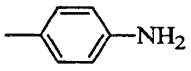


Table 2

Ex. No.	Ring A	R1	Physicochemical properties
4			m.p. 140-141°C
5			m.p. 160-161°C
6 (1)			not purified
6 (2)**			m.p. 186-190°C (decomp.)
7**			m.p. 184-185°C (decomp.)
8			m.p. 204-206°C
9*			m.p. 146-148°C (decomp.)

*: monohydrochloride **: dihydrochloride
Fmoc: 9-fluorenylmethyloxycarbonyl group

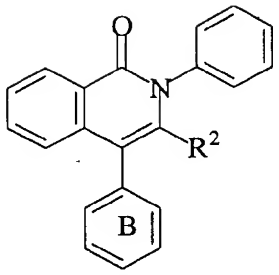
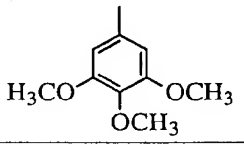
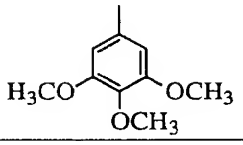
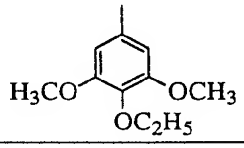
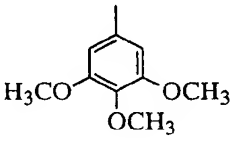
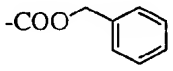
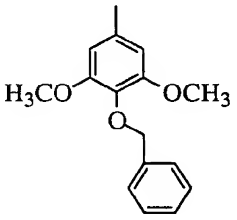
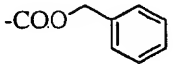
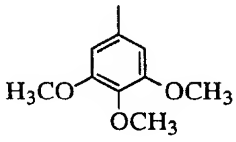
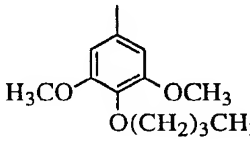


Table 3

Ex. No.	Ring B	R^2	Physicochemical properties
10		$-COOCH_3$	m.p. 190-191°C
11		$-COOC_2H_5$	m.p. 169-170°C
11a		$-COOC_2H_5$	m.p. 141-143°C
12			m.p. 145-147°C
12a			m.p. 128-130°C
13		$-COO(CH_2)_3CH_3$	m.p. 144-146°C
13a		$-COO(CH_2)_3CH_3$	m.p. 76-78°C

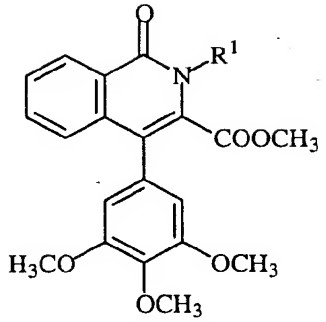


Table 4 (No. 1)

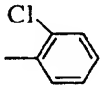
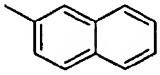
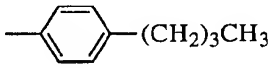
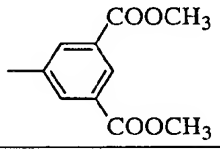
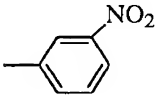
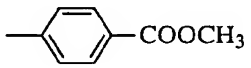
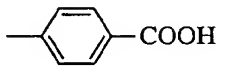
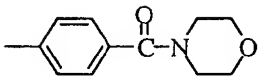
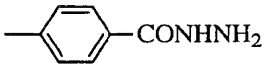
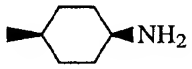
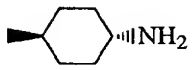
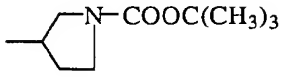
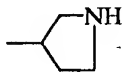
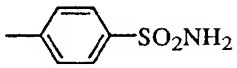
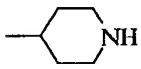
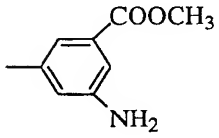
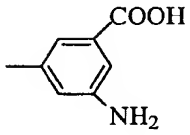
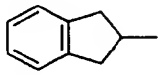
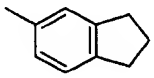
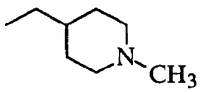
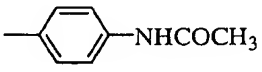
Ex. No.	R^1	Physicochemical properties
14		m.p. 177-179°C
15		m.p. 229-231°C
16		m.p. 145-147°C
17		m.p. 212-214°C
18		m.p. 204-206°C
19	$-N(CH_3)_2$	m.p. 173-175°C

Table 4 (No. 2)

Ex. No.	R^1	Physicochemical properties
20		m.p. 213-215°C
21 (1) (2)****		(1)m.p. 254-256°C (2)m.p. 259-261°C (decomp.)
22		m.p. 215-217°C
23		m.p. 223-225°C (decomp.)
24*		m.p. 175-177°C (decomp.)
25	 (cis)	m.p. 182-183°C
26	 (trans)	m.p. 217-218°C
27*		m.p. 167-169°C (decomp.)
28*		m.p. 255-257°C (decomp.)
29		m.p. 141-142°C

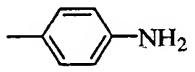
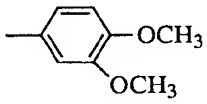
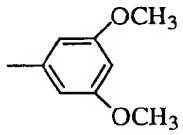
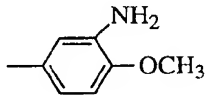
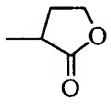
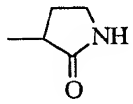
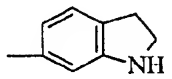
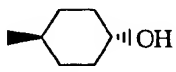
*: monohydrochloride
****: sodium salt

Table 4 (No. 3)

Ex. No.	R^1	Physicochemical properties
30*		m.p. 214-216°C (decomp.)
31		m.p. 258-260°C
32		m.p. 120-122°C
33		m.p. 186-189°C
34		m.p. 180-181°C
35		m.p. 156-157°C
36		m.p. 204-207°C
37		m.p. 223-224°C
38		m.p. 178-184°C
39		m.p. 198-202°C

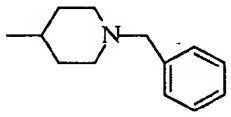
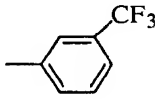
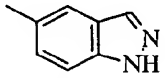
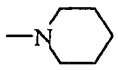
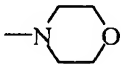
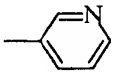
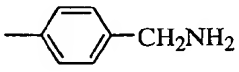
*: monohydrochloride

Table 4 (No. 4)

Ex. No.	R^1	Physicochemical properties
40*		m.p. 164-168°C (decomp.)
41		m.p. 190-192°C
42		m.p. 170-172°C
43*		m.p. 174-178°C (decomp.)
44		m.p. 213-215°C
45		m.p. >220°C
46*		m.p. 170-178°C (decomp.)
47		m.p. 172-173°C
48		m.p. 165-166°C
49	$-C_2H_5$	m.p. 171-173°C

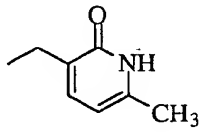
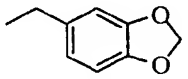
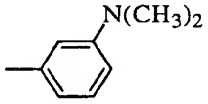
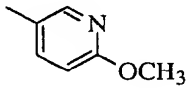
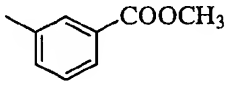
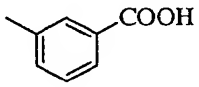
*: monohydrochloride

Table 4 (No. 5)

Ex. No.	R^1	Physicochemical properties
50		m.p. 166-168°C
51		m.p. 120-123°C
52		m.p. 244-246°C
53		m.p. 174-175°C
54	$-(CH_2)_3OH$	m.p. 148-150°C
55*		m.p. 245-247°C (decomp.)
56		m.p. 163-165°C
57		m.p. 173-175°C
58		m.p. 137-140°C
59*		m.p. 230-233°C (decomp.)

*: monohydrochloride

Table 4 (No. 6)

Ex. No.	R^1	Physicochemical properties
60		m.p. 214-215°C
61		m.p. 125-127°C
62*		m.p. 137-139°C (decomp.)
63*		m.p. 85-86°C
64		m.p. 207-208°C
65		m.p. 268-269°C

*: monohydrochloride

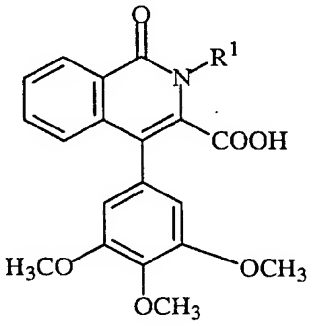


Table 5

Ex. No.	R^1	Physicochemical properties
66	$-NHCOOC(CH_3)_3$	m.p. 200-201°C (decomp.)

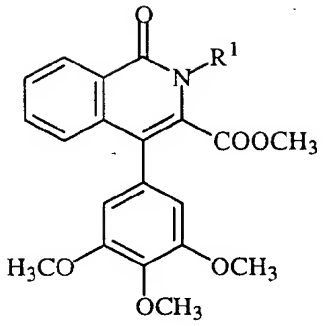
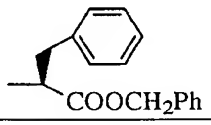
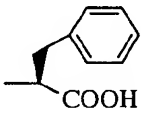
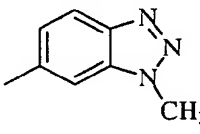


Table 6

Ex. No.	R^1	Physicochemical properties
67	$-NHCOOC(CH_3)_3$	m.p. 206-208°C
68	$-NH_2$	m.p. 209-211°C
69	$-NHCOCH_3$	m.p. 136-139°C
70	$-N(COCH_3)_2$	m.p. 184-185°C
71	$-N(CH_3)(COOC(CH_3)_3)$	–
72	$-NHCH_3$	m.p. 218-220°C
73	$-N(CH_2CH_2OH)(COOC(CH_3)_3)$	–
74	$-NHCH_2CH_2OH$	m.p. 167-168°C
75	$-NHCH_2CH_2OCOCH_3$	m.p. 126-127°C
76	$-NHCH_2CH_2CH_3$	m.p. 147-148°C
77	$-NHCH_2CH_3$	m.p. 149-151°C
78		–
79		m.p. 191-194°C
80		m.p. 155-157°C

Ph: phenyl group

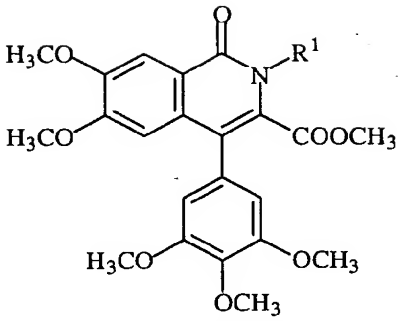


Table 7 (No. 1)

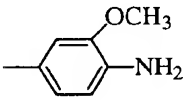
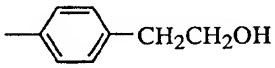
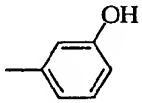
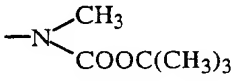
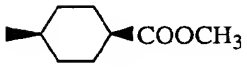
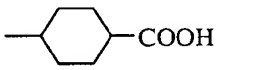
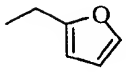
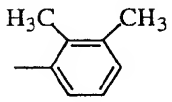
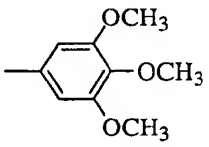
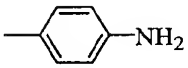
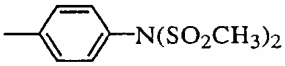
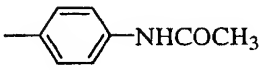
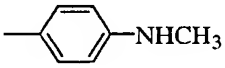
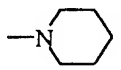
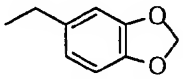
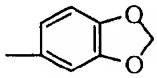
Ex. No.	R^1	Physicochemical properties
81		m.p. 199-200°C
82		m.p. 238-239°C
83		m.p. 148-152°C
84		m.p. 230-231°C
85		-

Table 7 (No. 2)

Ex. No.	R^1	Physicochemical properties
86	$-NHCH_3$	m.p. 189-190°C
87	 (cis)	m.p. 110-113°C
88		m.p. 193-198°C
89		m.p. 142-143°C
90		m.p. 202-203°C
91		m.p. 232-233°C
92 (1) (2)*		(1)m.p. 203-205°C (2)m.p. >230
93		m.p. >230°C
94		m.p. 235-237°C
95		m.p. 239-241°C

*: monohydrochloride

Table 7 (No. 3)

Ex. No.	R^1	Physicochemical properties
96		m.p. 125-128°C
97		m.p. 185-186°C
98		m.p. >250°C

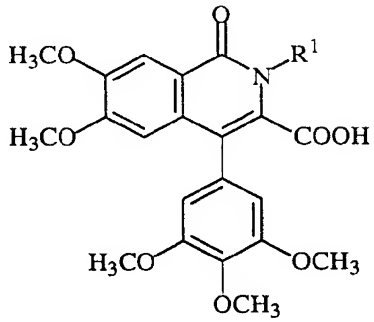
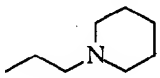


Table 8

Ex. No.	R^1	Physicochemical properties
99 (1) (2)****	H	(1)m.p. >250°C (2)m.p. >250°C
100		m.p. 198-200°C

****: sodium salt

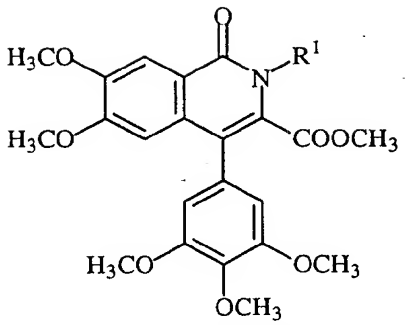


Table 9 (No. 1)

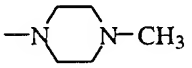
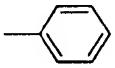
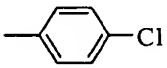
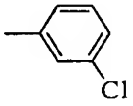
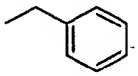
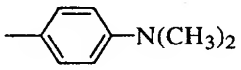
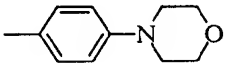
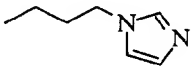
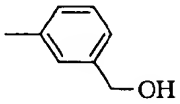
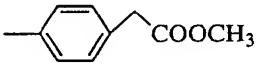
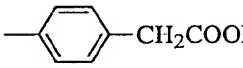
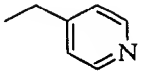
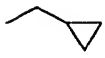
Ex. No.	R^1	Physicochemical properties
101		m.p. >250°C
102		m.p. 214-216°C
103		m.p. 194-195°C
104		m.p. 233-235°C
105		m.p. 132-134°C

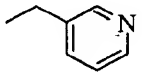
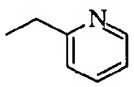
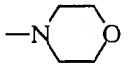
Table 9 (No. 2)

Ex. No.	R^1	Physicochemical properties
106		m.p. 182-183°C
107*		m.p. 226-228°C
108*		m.p. 223-227°C (decomp.)
109		m.p. 158-160°C
110		m.p. 204-205°C
111		m.p. 187-188°C
112****		m.p. 132-136°C (decomp.)
113	–H	m.p. 204-207°C
114*		m.p. 218-220°C (decomp.)
115		m.p. 117-119°C

*: monohydrochloride

****: sodium salt

Table 9 (No. 3)

Ex. No.	R^1	Physicochemical properties
116*		m.p. 209-211°C (decomp.)
117*		m.p. 155-157°C (decomp.)
118		m.p. 219-220°C

*: monohydrochloride

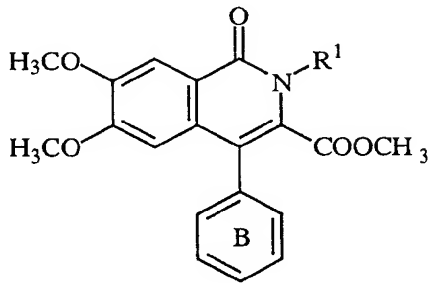
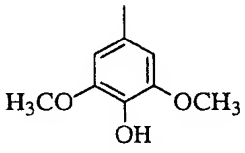
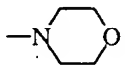


Table 10

Ex. No.	Ring B	R^1	Physicochemical properties
119			m.p. >250°C

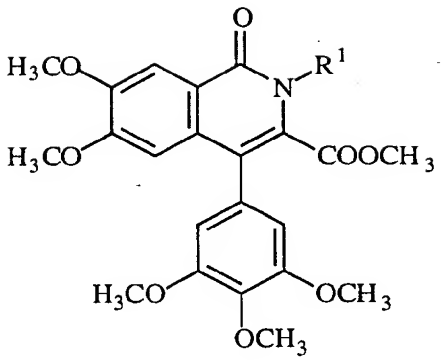
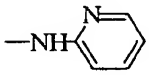
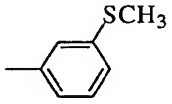
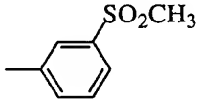
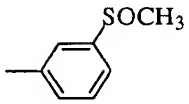
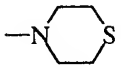
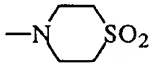
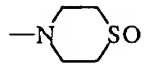


Table 11

Ex. No.	R^1	Physicochemical properties
120*		m.p. 178-179°C (decomp.)
121		m.p. 217-218°C
122		m.p. >250°C
123		m.p. 241-244°C
124		m.p. 215-218°C
125		m.p. 226-227°C (decomp.)
126		m.p. >250°C

*: monohydrochloride

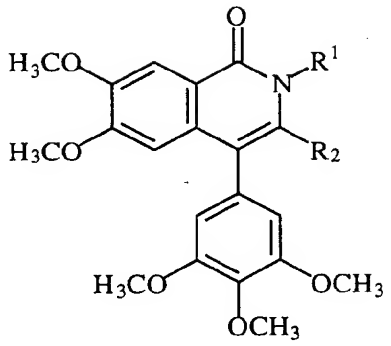
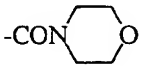
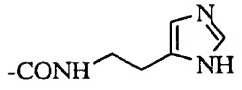
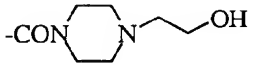
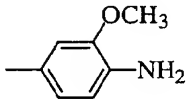


Table 12

Ex. No.	R^1	R^2	Physicochemical properties
127	$-CH_3$	$-COOCH_3$	m.p. 170-171°C
128	$-CH_3$	-COOH	m.p. >270°C
129	$-CH_3$		m.p. 188-190°C
130	$-CH_3$		m.p. >210°C
131	$-CH_3$		m.p. 133-134°C
132		$-COOCH_2Si(CH_3)_3$	m.p. 191-192°C

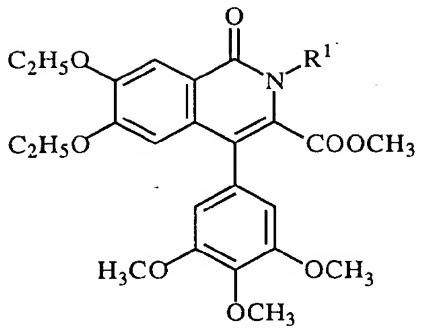
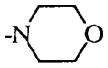
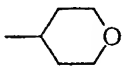
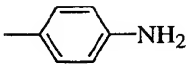
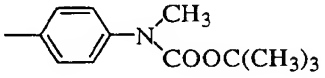
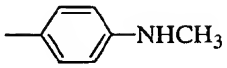
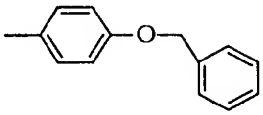
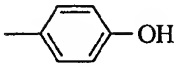


Table 13

Ex. No.	R^1	Physicochemical properties
133		m.p. 195-197°C
134		m.p. 182-184°C
135		m.p. 204-206°C
136 (1)* (2)		(1)m.p. 222-225°C (decomp.) (2)m.p. 170-172°C
137		m.p. 161-163°C
138*		m.p. 206-208°C (decomp.)
139		m.p. 145-147°C
140		m.p. 197-199°C

*: monohydrochloride

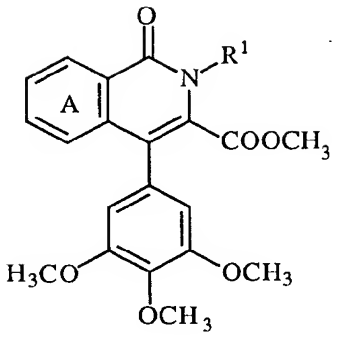


Table 14 (No. 1)

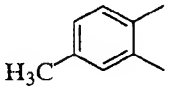
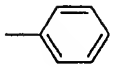
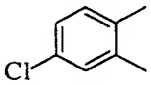
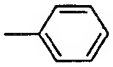
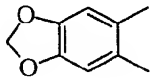
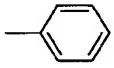
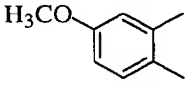
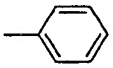
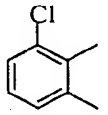
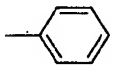
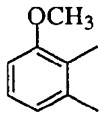
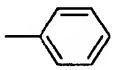
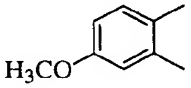
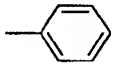
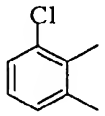
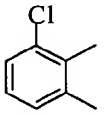
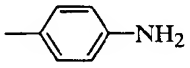
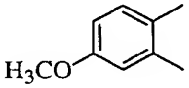
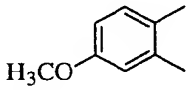
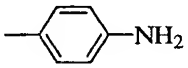
Ex. No.	Ring A	R1	Physicochemical properties
141			m.p. 169-170°C
142			m.p. 196-198°C
143			m.p. 223-225°C
144			m.p. 209-211°C
145			m.p. 182-183°C

Table 14 (No. 2)

Ex. No.	Ring A	R^1	Physicochemical properties
146			m.p. 216-217°C
147			m.p. 206-208°C
148			m.p. 235-237°C
149*			m.p. 210-212°C (decomp.)
150			m.p. 235-237°C (decomp.)
151			m.p. 210-211°C

*: monohydrochloride

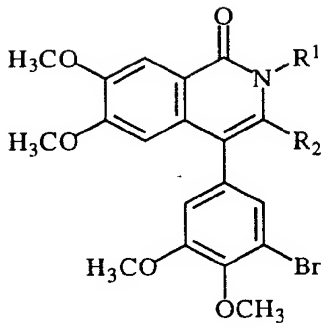
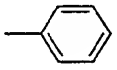
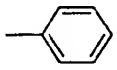
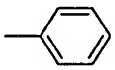
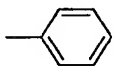


Table 15

Ex. No.	R^1	R^2	Physicochemical properties
152		-COOH	m.p. 184-186°C
153		$-COOCH_3$	m.p. 223-225°C
154		$-CONH_2$	m.p. 258-261°C
155		$-CONHCH_3$	m.p. 249-252°C

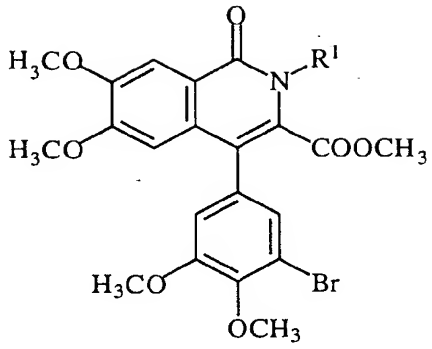


Table 16 (No. 1)

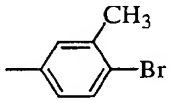
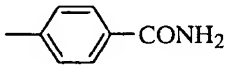
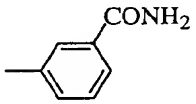
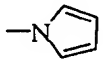
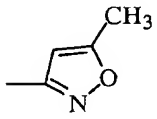
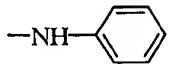
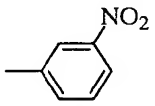
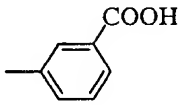
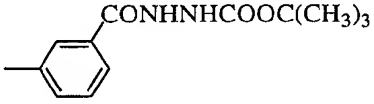
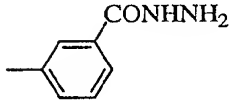
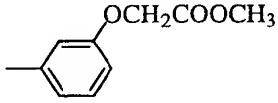
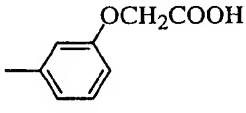
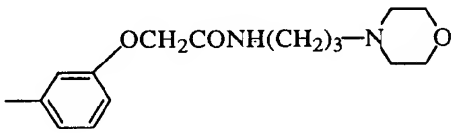
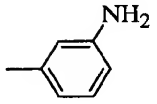
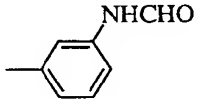
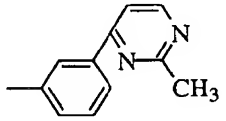
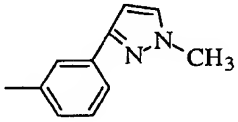
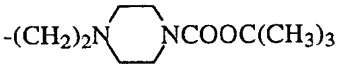
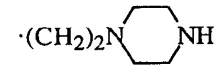
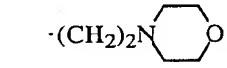
Ex. No.	R^1	Physicochemical properties
156		m.p. 198-200°C
157		m.p. >250°C
158		m.p. 261-263°C
159	$-CH_2COOCH_3$	m.p. 185-186°C
160	$-CH_2COOC_2H_5$	m.p. 156-157°C
161	$-CH_2COOH$	m.p. 200-202°C
162	$-C_2H_4OC_2H_4OH$	m.p. 144-146°C
163		m.p. 224-225°C
164	$-C_2H_4NHCOOC(CH_3)_3$	m.p. 174-176°C

Table 16 (No. 2)

Ex. No.	R^1	Physicochemical properties
165*	$-C_2H_4NH_2$	m.p. 188-190°C (decomp.)
166		m.p. 209-211°C
167		m.p. 132-135°C
168		m.p. 245-246°C
169	$-C_2H_4OCH_3$	m.p. 154-156°C
170		m.p. 246-247°C
171		m.p. 201-202°C
172		m.p. 162-163°C
173		m.p. 184-185°C
174		m.p. 252-253°C

*: monohydrochloride

Table 16 (No. 3)

Ex. No.	R^1	Physicochemical properties
175		m.p. 118-119°C
176		m.p. 241-242°C
177		m.p. >250°C
178		m.p. 131-132°C
179		m.p. 211-212°C
180		m.p. 153-154°C
181**		m.p. 210-211°C (decomp.)
182*		m.p. 216-217°C (decomp.)
183	$-NH_2$	m.p. 215-216°C
184	$-(CH_2)_3OH$	m.p. 105-106°C

*: monohydrochloride
**: dihydrochloride

Table 16 (No. 4)

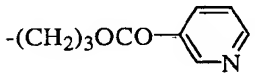
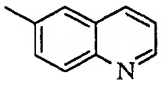
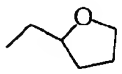
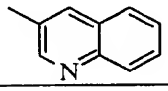
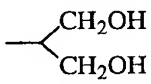
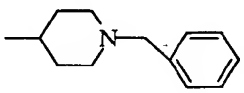
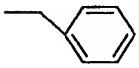
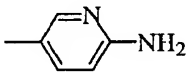
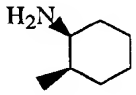
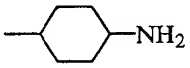
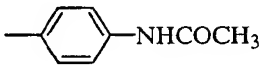
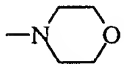
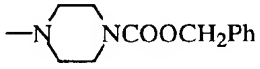
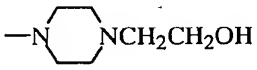
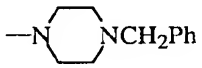
Ex. No.	R^1	Physicochemical properties
185		m.p. 119-120°C
186	$-(CH_2)_3CH_3$	m.p. 140-141°C
187	$-CH_2CONH_2$	m.p. 213-216°C
188		m.p. >230°C
189		m.p. 180-182°C
190		m.p. 122-124°C
191		m.p. 193-196°C
192	$-(CH_2)_3N(CH_3)_2$	m.p. 151-154°C
193	$-(CH_2)_3NHCOOC(CH_3)_3$	m.p. 129-132°C
194	$-(CH_2)_3OCH_3$	m.p. 138-140°C

Table 16 (No. 5)

Ex. No.	R^1	Physicochemical properties
195		m.p. 129-131°C
196		m.p. 187-189°C
197	$-(CH_2)_2CH_3$	m.p. 166-168°C
198		m.p. 223-226°C (decomp.)
199*	$-(CH_2)_4NH_2$	m.p. 172-178°C (decomp.)
200*		m.p. 210-214°C (decomp.)
201*		m.p. 189-192°C (decomp.)
202		m.p. 192-194°C
203		m.p. 195-196°C
204		m.p. 218-222°C

*: monohydrochloride
Ph: phenyl group

Table 16 (No. 6)

Ex. No.	R^1	Physicochemical properties
205*		m.p. 244-246°C (decomp.)
206		m.p. 135-136°C
207*	$-(CH_2)_3NH_2$	m.p. 210-212°C (decomp.)

*: monohydrochloride
Ph: phenyl group

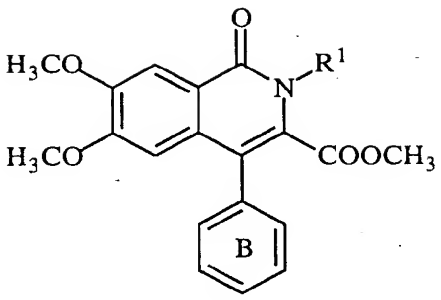
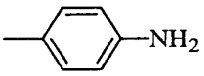
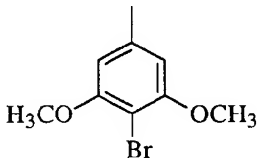
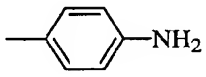
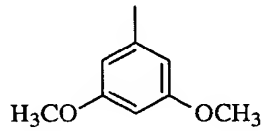
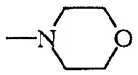
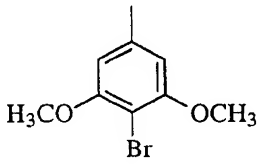
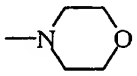
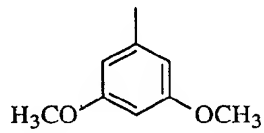
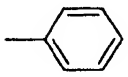
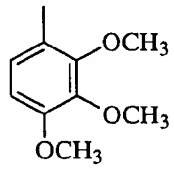


Table 17

Ex. No.	R^1	Ring B	Physicochemical properties
208*			m.p. >230°C
209*			m.p. >230°C
210			m.p. >230°C
211			m.p. 206-208°C
212			m.p. 239-241°C

*: monohydrochloride

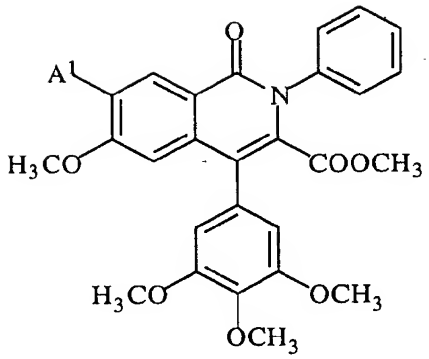
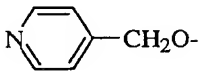
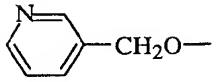
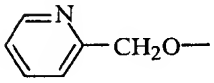
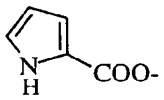
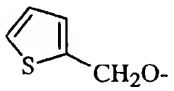
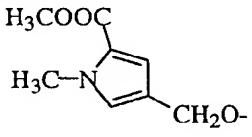


Table 18

Ex. No.	A^1	Physicochemical properties
213	$PhCH_2O$-	m.p. 235-237°C
214	HO-	m.p. 210-212°C
215*		m.p. 151-152°C
216*		m.p. 145-146°C
217*		m.p. 107-109°C
218		m.p. 234-235°C
219		m.p. 215-216°C
220		m.p. 193-195°C

*: monohydrochloride
Ph: phenyl group

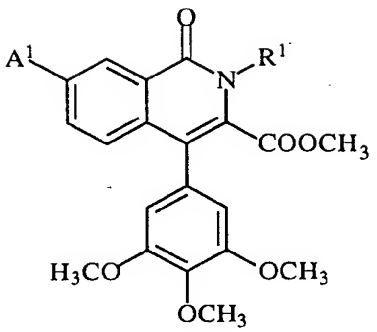
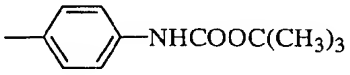
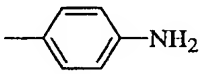
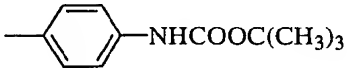
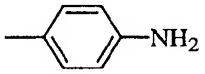
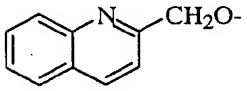
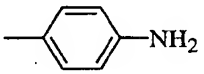
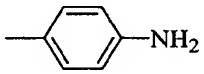
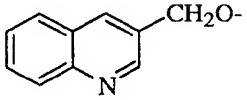
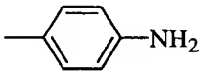


Table 19

Ex. No.	A^1	R^1	Physicochemical properties
221	$PhCH_2O$-		m.p. 148-149°C
222*	$PhCH_2O$-		m.p. 207-208°C (decomp.)
223	HO-		m.p. 230-231°C
224*	HO-		m.p. 254-255°C (decomp.)
225**			m.p. 194-197°C (decomp.)
226**			m.p. 193-197°C (decomp.)
227**			m.p. 203-206°C (decomp.)

*: monohydrochloride
**: dihydrochloride
Ph: phenyl group

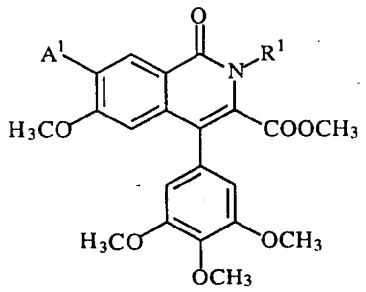
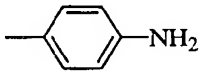
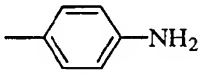
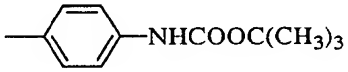
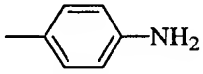
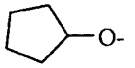
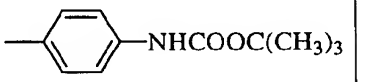
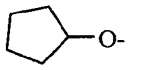
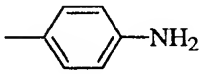
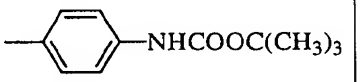
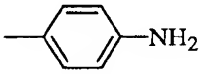
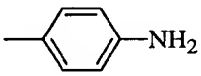
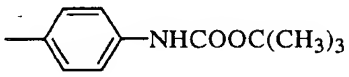
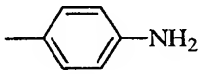
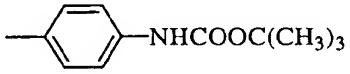
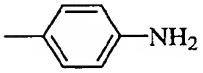
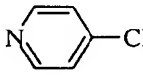
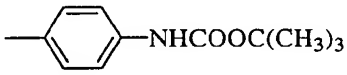
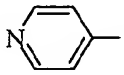
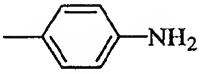
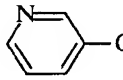
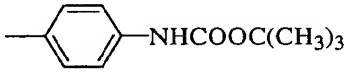
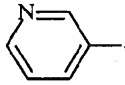
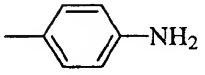


Table 20 (No. 1)

Ex. No.	A^1	R^1	Physicochemical properties
228	$PhCH_2O$-		m.p. 161-163°C (decomp.)
229	HO-		m.p. 170-172°C (decomp.)
230(1)	$(CH_3)_3COOCCH_2O$-		m.p. 203-204°C
230(2)*	$HOOCCH_2O$-		m.p. 170-172°C (decomp.)
231(1)			m.p. 156-158°C
231(2)*			m.p. 168-170°C (decomp.)
232(1)	$(CH_3)_2NCH_2CH_2O$-		m.p. 203-204°C
232(2)**	$(CH_3)_2NCH_2CH_2O$-		m.p. >220°C
233(1)	$CH_3O(CH_2)_2O(CH_2)_2O$-		m.p. 152-154°C
233(2)*	$CH_3O(CH_2)_2O(CH_2)_2O$-		m.p. 138-145°C (decomp.)

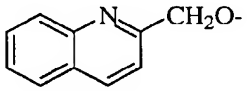
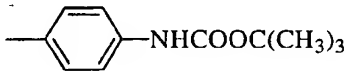
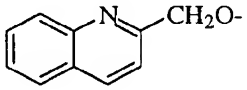
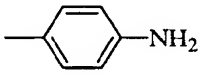
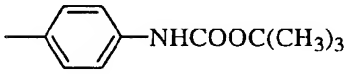
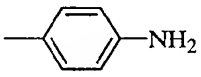
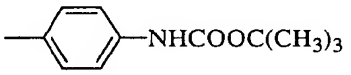
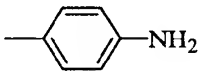
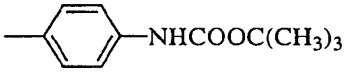
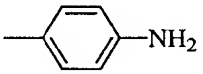
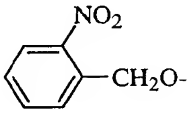
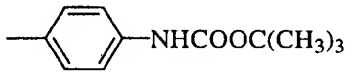
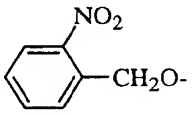
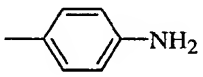
*: monohydrochloride
**: dihydrochloride
Ph: phenyl group

Table 20 (No. 2)

Ex. No.	A^1	R^1	Physicochemical properties
234(1)	CH_3CH_2O-		m.p. 227-229°C
234(2)*	CH_3CH_2O-		m.p. 197-200°C (decomp.)
235(1)	$CH_3O(CH_2)_2O$-		m.p. 245-247°C
235(2)	$CH_3O(CH_2)_2O$-		m.p. 165-170°C (decomp.)
236(1)			m.p. 143-145°C
236(2)**			m.p. 191-196°C (decomp.)
237(1)			m.p. 131-132°C
237(2)**			m.p. 186-190°C (decomp.)

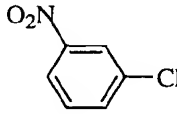
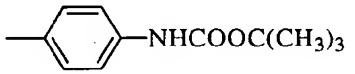
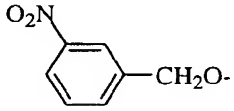
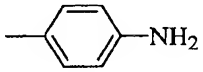
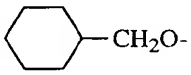
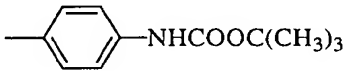
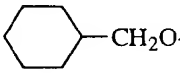
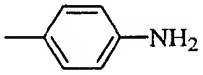
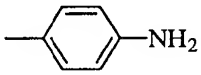
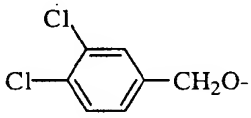
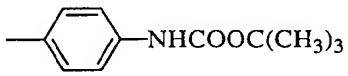
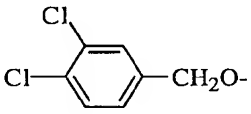
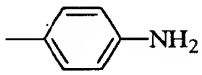
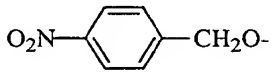
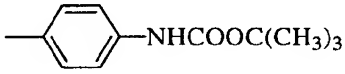
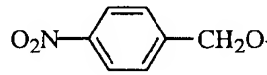
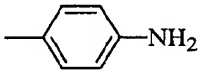
*: monohydrochloride
**: dihydrochloride

Table 20 (No. 3)

Ex. No.	A^1	R^1	Physicochemical properties
238(1)			m.p. 172-173°C
238(2)**			m.p. 183-186°C (decomp.)
239(1)	$HO(CH_2)_2O$-		m.p. 139-140°C
239(2)*	$HO(CH_2)_2O$-		m.p. 174-176°C (decomp.)
240(1)	$Ph(CH_2)_2O$-		m.p. 224-225°C
240(2)*	$Ph(CH_2)_2O$-		m.p. 146-149°C (decomp.)
241(1)	$PhCOCH_2O$-		m.p. 218-219°C
241(2)*	$PhCOCH_2O$-		m.p. 175-177°C (decomp.)
242(1)			m.p. 149-151°C
242(2)*			m.p. 154-156°C (decomp.)

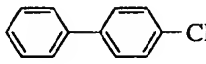
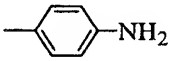
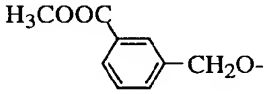
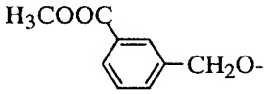
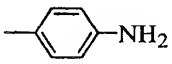
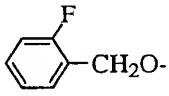
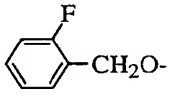
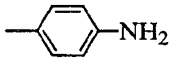
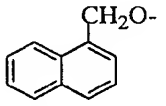
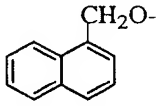
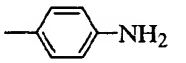
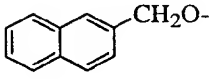
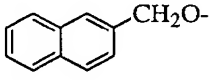
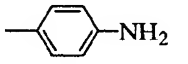
*: monohydrochloride
**: dihydrochloride
Ph: phenyl group

Table 20 (No. 4)

Ex. No.	A^1	R^1	Physicochemical properties
243(1)			m.p. 138-139°C
243(2)*			m.p. 225-227°C (decomp.)
244(1)			Powder
244(2)*			m.p. 166-167°C (decomp.)
245(1)	$H_3COOCCH_2O$-		m.p. 205-206°C
245(2)*	$H_3COOCCH_2O$-		m.p. 195-197°C (decomp.)
246(1)			m.p. 193-195°C
246(2)*			m.p. 237-239°C (decomp.)
247(1)			m.p. 183-185°C
247(2)*			m.p. 235-237°C (decomp.)

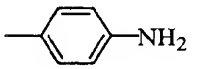
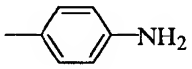
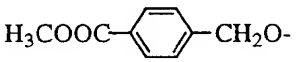
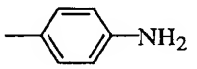
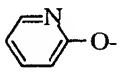
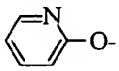
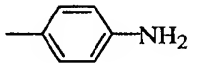
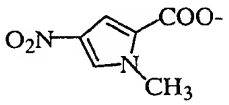
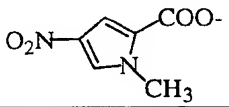
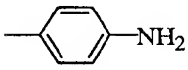
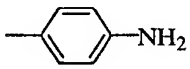
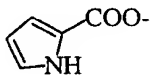
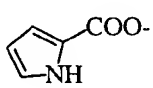
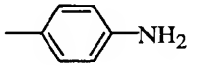
*: monohydrochloride

Table 20 (No. 5)

Ex. No.	A^1	R^1	Physicochemical properties
248(1)			m.p. 216-217°C
248(2)*			m.p. 151-153°C (decomp.)
249(1)			m.p. 190-191°C
249(2)*			m.p. 205-208°C (decomp.)
250(1)			m.p. 176-178°C
250(2)*			m.p. 167-169°C (decomp.)
251(1)			m.p. 230-232°C (decomp.)
251(2)*			m.p. 156-158°C (decomp.)
252(1)			m.p. 216-217°C
252(2)*			m.p. 185-190°C (decomp.)

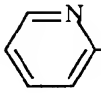
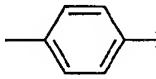
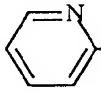
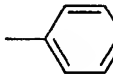
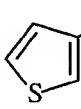
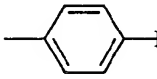
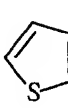
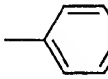
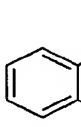
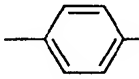
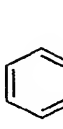
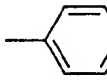
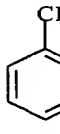
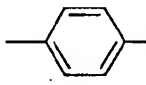
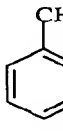
*: monohydrochloride

Table 20 (No. 6)

Ex. No.	A^1	R^1	Physicochemical properties
253(1)	$CH_2=CHCH_2O$-		m.p. 229-230°C
253(2)*	$CH_2=CHCH_2O$-		m.p. 197-200°C (decomp.)
254(2)*			m.p. >230°C
254(3)*			m.p. 192-195°C (decomp.)
255(1)			m.p. 223-224°C
255(2)**			m.p. 186-188°C (decomp.)
256(1)			m.p. 232-233°C
256(2)*			m.p. 220-223°C (decomp.)
257(1)	PhCOO-		m.p. 234-235°C
257(2)*	PhCOO-		m.p. 175-176°C (decomp.)
258(1)			–
258(2)*			m.p. 180-182°C (decomp.)

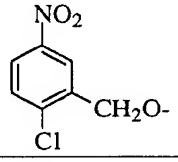
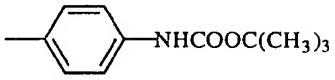
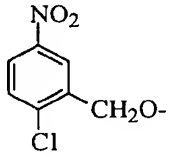
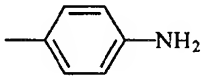
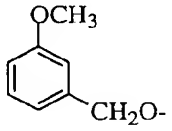
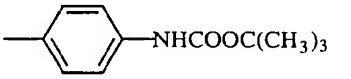
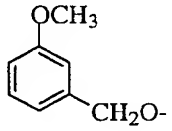
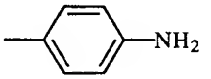
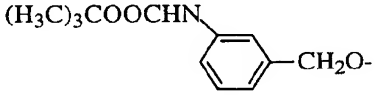
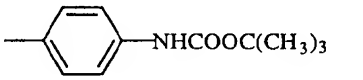
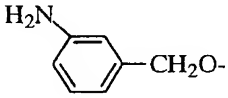
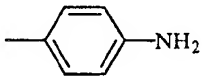
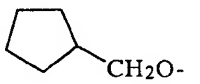
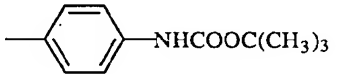
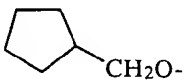
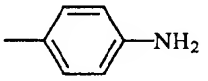
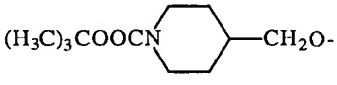
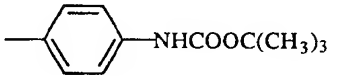
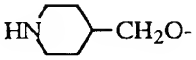
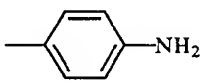
*: monohydrochloride
**: dihydrochloride
Ph: phenyl group

Table 20 (No. 7)

Ex. No.	A^1	R^1	Physicochemical properties
259(1)			m.p. 213-215°C
259(2)**			m.p. 178-182°C (decomp.)
260(1)			m.p. 143-145°C
260(2)*			m.p. 151-155°C (decomp.)
261(1)			m.p. 145-146°C
261(2)**			m.p. 196-200°C (decomp.)
262(1)			m.p. 142-144°C
262(2)*			m.p. 165-168°C (decomp.)

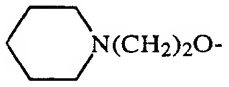
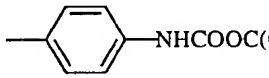
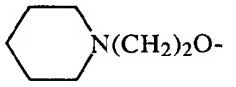
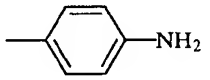
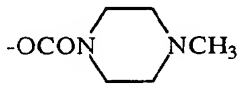
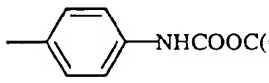
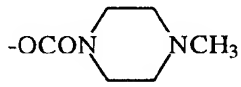
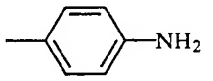
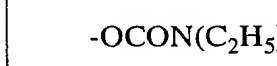
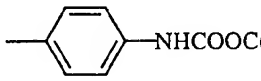
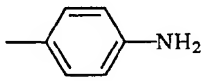
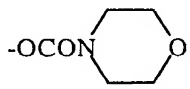
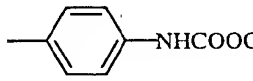
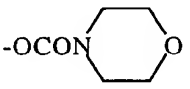
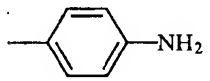
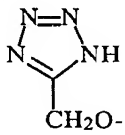
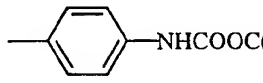
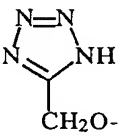
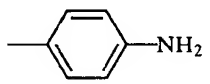
*: monohydrochloride
**: dihydrochloride

Table 20 (No. 8)

Ex. No.	A^1	R^1	Physicochemical properties
263(1)			m.p. 138-139°C
263(2)*			m.p. 159-160°C (decomp.)
264(1)			–
264(2)*			m.p. 160-164°C (decomp.)
265(1)			–
265(2)**			m.p. 218-219°C (decomp.)
266(1)			–
266(2)*			m.p. 161-162°C (decomp.)
267(1)			m.p. 116-119°C
267(2)**			m.p. 225-227°C (decomp.)

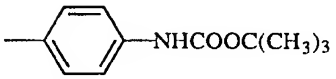
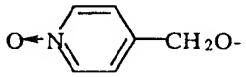
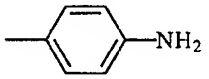
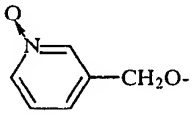
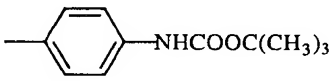
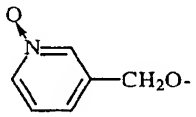
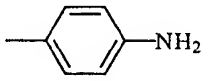
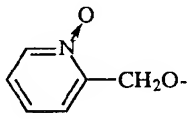
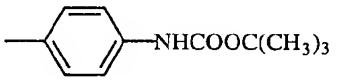
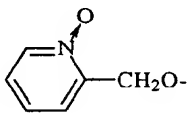
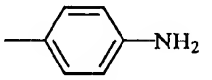
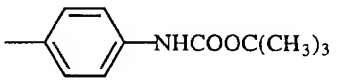
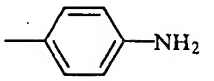
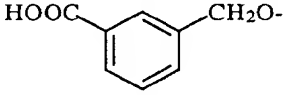
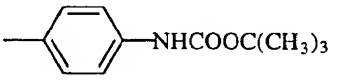
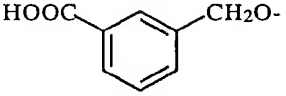
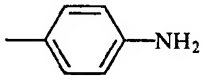
*: monohydrochloride
**: dihydrochloride

Table 20 (No. 9)

Ex. No.	A^1	R^1	Physicochemical properties
268(1)			m.p. 209-210°C
268(2)**			m.p. 83-84°C (decomp.)
269(1)			m.p. 245-247°C (decomp.)
269(2)**			m.p. 216-218°C (decomp.)
270(1)			m.p. 237-240°C (decomp.)
270(2)*			m.p. 186-188°C (decomp.)
271(1)			m.p. >250°C
271(2)*			m.p. 179-180°C (decomp.)
272(2)			m.p. 193-194°C
272(3)*			m.p. >230°C

*: monohydrochloride
**: dihydrochloride

Table 20 (No. 10)

Ex. No.	A^1	R^1	Physicochemical properties
273(1)			m.p. 159-160°C
273(2)*			m.p. 178-180°C (decomp.)
274(1)			m.p. 141-142°C
274(2)*			m.p. 177-179°C (decomp.)
275(1)			m.p. 148-149°C
275(2)*			m.p. 180-183°C (decomp.)
276(1)	$-OCH_2CONH_2$		m.p. 227-228°C
276(2)*	$-OCH_2CONH_2$		m.p. 195-197°C (decomp.)
277(1)			–
277(2)*			m.p. 171-174°C (decomp.)

*: monohydrochloride

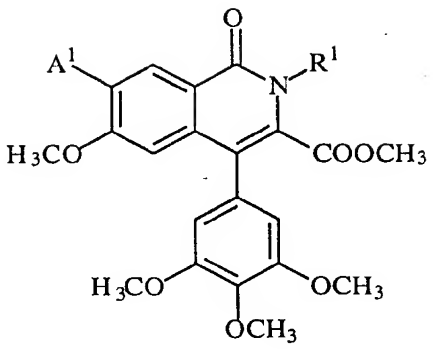
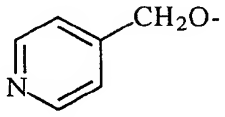
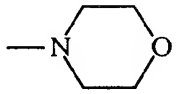
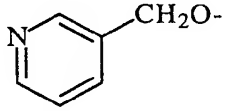
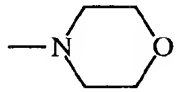


Table 21

Ex. No.	A^1	R^1	Physicochemical properties
278*			m.p. 221-223°C (decomp.)
279*			m.p. 108-110°C (decomp.)

*: monohydrochloride

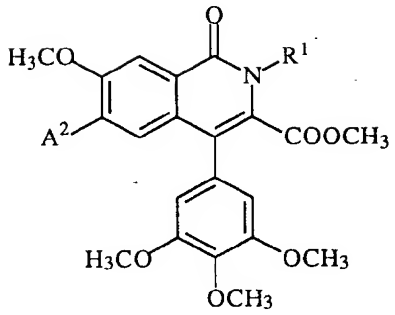
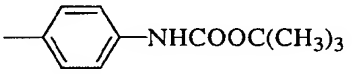
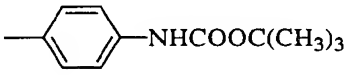
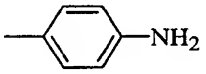
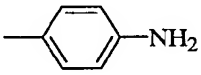
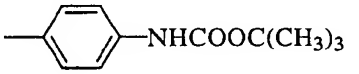
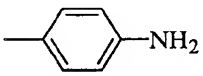
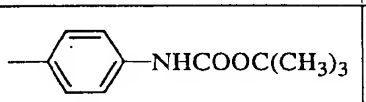
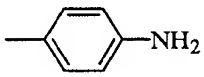
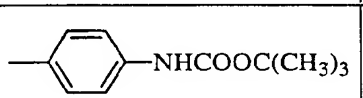
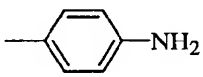
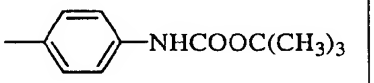
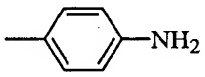
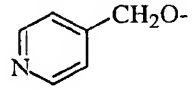
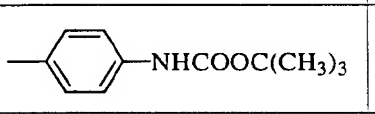
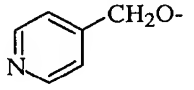
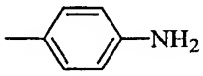
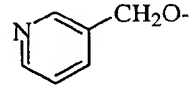
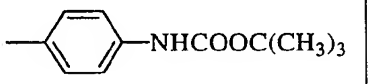
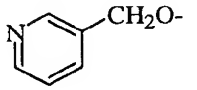
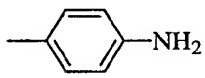
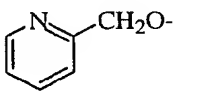
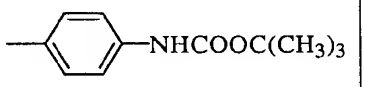
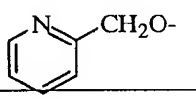
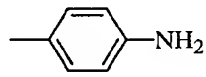
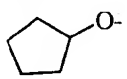
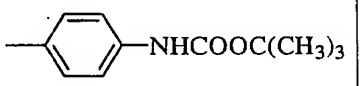
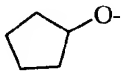
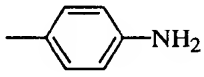
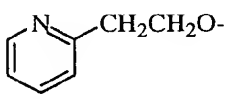
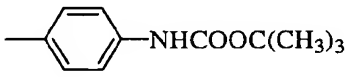
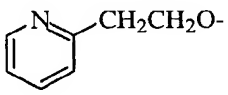
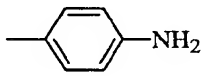


Table 22 (No. 1)

Ex. No.	A^2	R^1	Physicochemical properties
280	$PhCH_2O$-		m.p. 198-199°C
281	HO-		m.p. 228-229°C
282*	$PhCH_2O$-		m.p. 174-177°C (decomp.)
283*	HO-		m.p. 175-180°C (decomp.)
284(1)	$CH_3O(CH_2)_2O(CH_2)_2O$-		m.p. 200-202°C
284(2)*	$CH_3O(CH_2)_2O(CH_2)_2O$-		m.p. 175-180°C (decomp.)
285(1)	CH_3CH_2O-		m.p. 196-198°C
285(2)*	CH_3CH_2O-		m.p. 189-190°C (decomp.)
286(1)	$CH_3O(CH_2)_2O$-		m.p. 186-187°C
286(2)*	$CH_3O(CH_2)_2O$-		m.p. 205-210°C (decomp.)

*: monohydrochloride
**: dihydrochloride
Ph: phenyl group

Table 22 (No. 2)

Ex. No.	A^2	R^1	Physicochemical properties
287(1)	$HO(CH_2)_2O$-		m.p. 138-139°C
287(2)*	$HO(CH_2)_2O$-		m.p. 195-200°C (decomp.)
288(1)			m.p. 219-221°C
288(2)**			m.p. 215-220°C (decomp.)
289(1)			m.p. 189-190°C
289(2)**			m.p. 208-210°C (decomp.)
290(1)			m.p. 171-173°C
290(2)**			m.p. 188-189°C (decomp.)
291(1)			m.p. 221-223°C
291(2)*			m.p. 160-162°C (decomp.)
292(1)			m.p. 202-203°C
292(2)**			m.p. 187-190°C (decomp.)

*: monohydrochloride
**: dihydrochloride

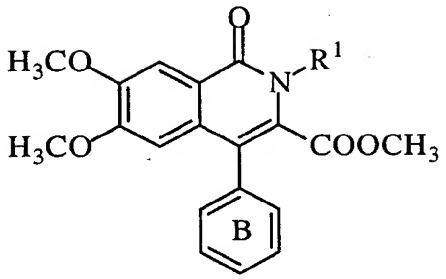
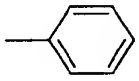
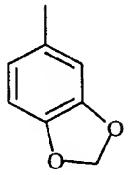
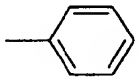
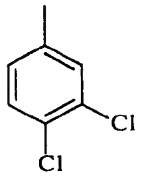


Table 23

Ex. No.	R^1	Ring B	Physicochemical properties
293			m.p. 234-235°C
294			m.p. 228-230°C

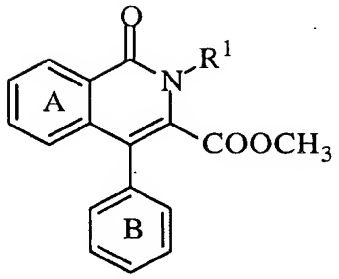
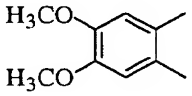
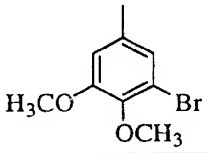
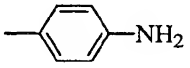
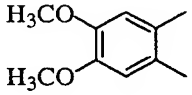
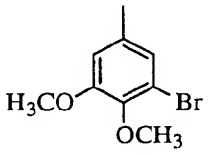
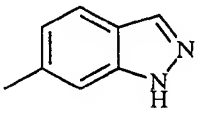
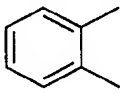
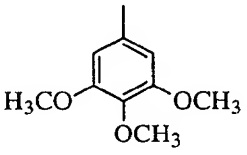
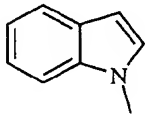
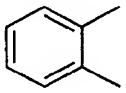
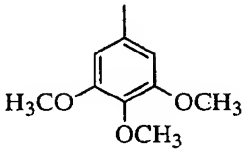
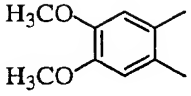
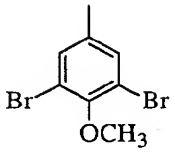
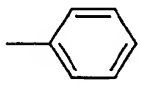


Table 24

Ex. No.	Ring A	Ring B	R1	Physicochemical properties
295*				m.p. >220°C
296				m.p. 168-171°C
297				m.p. 176-178°C
298			-NHCOCF3	m.p. 167-169°C
299				m.p. 189-191°C

*: monohydrochloride

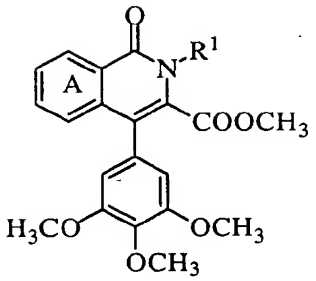
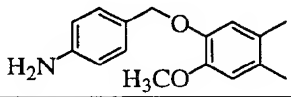
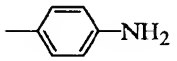
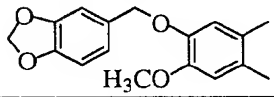
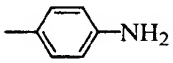
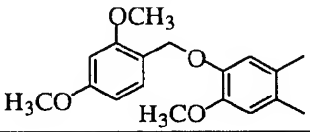
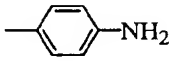
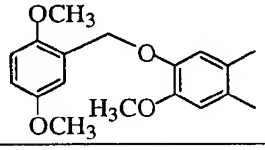
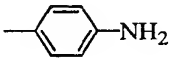
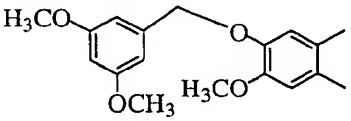
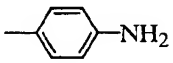
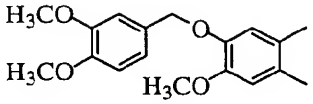
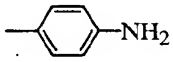
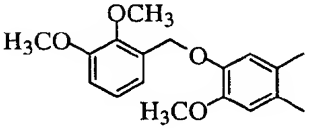
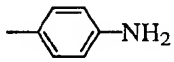
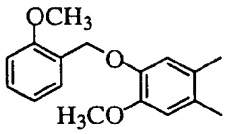
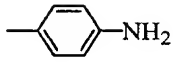
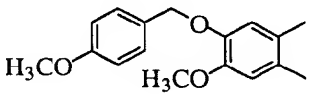
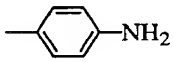


Table 25

Ex. No.	Ring A	R^1	Physicochemical properties
300**			m.p. 184-186 °C
301*			m.p. 165-168°C (decomp.)
302*			m.p. 138-141°C (decomp.)
303*			m.p. 228-231°C (decomp.)
304*			m.p. 214-217°C (decomp.)
305*			m.p. 136-138°C (decomp.)
306*			m.p. 144-146°C (decomp.)
307*			m.p. 146-148°C (decomp.)
308*			m.p. 141-144°C (decomp.)

*: monohydrochloride
**: dihydrochloride

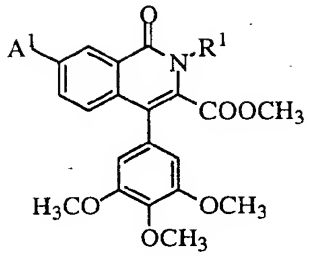
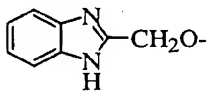
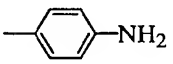
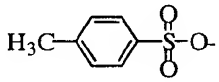
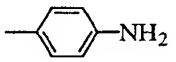
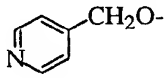
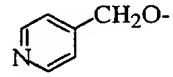
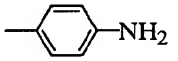
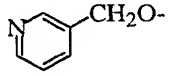
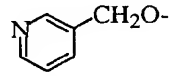
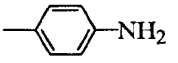
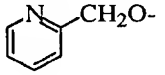
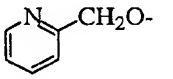
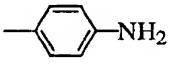
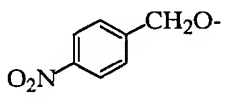
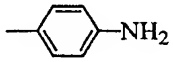
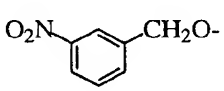
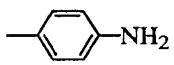
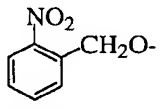
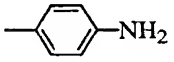


Table 26

Ex. No.	A^1	R^1	Physicochemical properties
309**			m.p. 242-243°C (decomp.)
310*			m.p. 190-195°C (decomp.)
311(1)			m.p. 150-151°C
311(2)**			m.p. 232-233°C (decomp.)
312(1)			m.p. 144-145°C
312(2)**			m.p. 208-209°C (decomp.)
313(1)			m.p. 136-138°C
313(2)**			m.p. 207-208°C (decomp.)
314*			m.p. 240-242°C (decomp.)
315*			m.p. 232-235°C (decomp.)
316*			m.p. 181-183°C (decomp.)

*: monohydrochloride, **: dihydrochloride

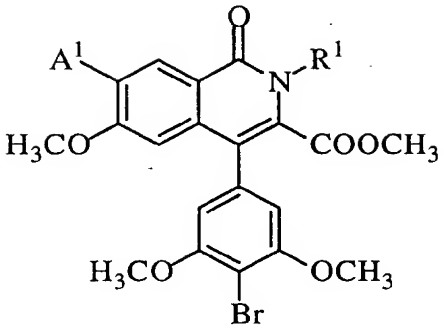
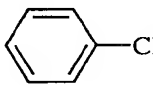
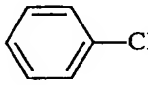
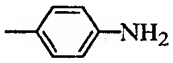
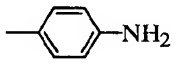
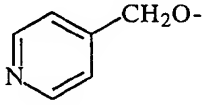
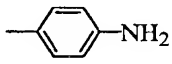
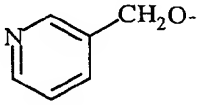
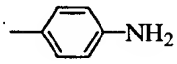
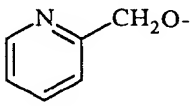
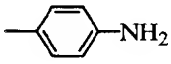
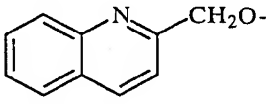
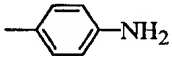


Table 27

Ex. No.	A^1	R^1	Physicochemical properties
317			m.p. 168-169°C
318*			m.p. 194-196°C (decomp.)
319(1) (2)*	HO-		(1)m.p. 171-172°C (2)m.p. 238-242°C (decomp.)
320**			m.p. 213-214°C (decomp.)
321**			m.p. 196-199°C (decomp.)
322**			m.p. 186-188°C (decomp.)
323**			m.p. 240-243°C (decomp.)

*: monohydrochloride
**: dihydrochloride

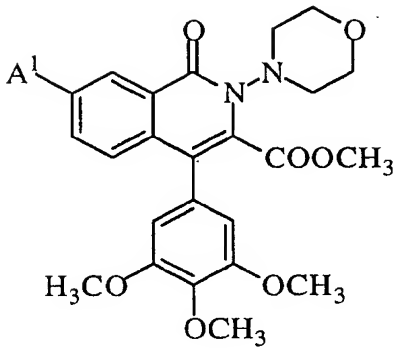
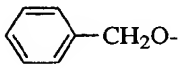
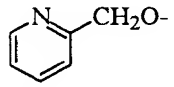
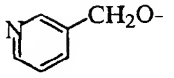
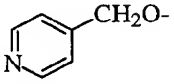


Table 28

Ex. No.	A^1	Physicochemical properties
324		m.p. 173-174°C
325	HO-	m.p. >250°C
326*		m.p. 193-196°C (decomp.)
327*		m.p. 135-138°C (decomp.)
328*		m.p. 138-139°C (decomp.)

*: monohydrochloride

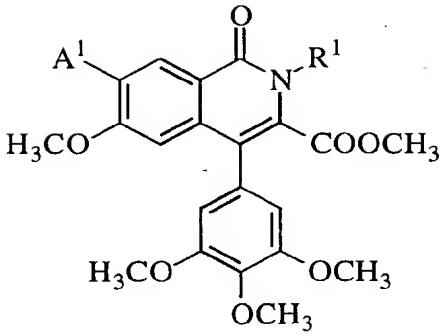
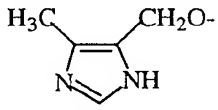
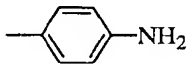
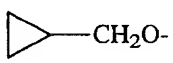
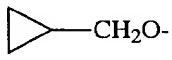
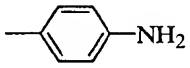
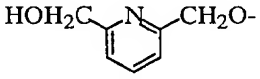
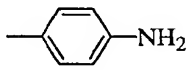
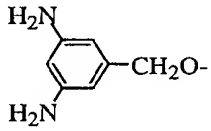
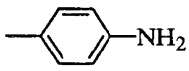
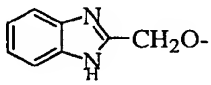
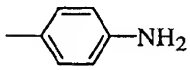


Table 29

Ex. No.	A^1	R^1	Physicochemical properties
329			m.p. 175-178°C (decomp.)
330(1)			m.p. 237-240°C (decomp.)
330(2)*			m.p. 210-212°C (decomp.)
331**			m.p. 193-195°C (decomp.)
332***			m.p. 210-212°C (decomp.)
333**			m.p. 210-215°C (decomp.)

*: monohydrochloride
**: dihydrochloride
***: trihydrochloride.

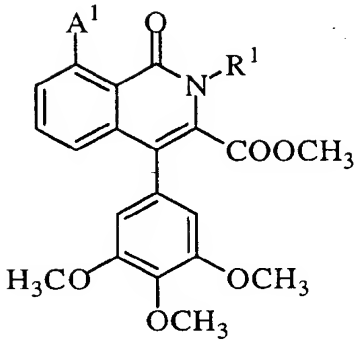
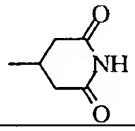
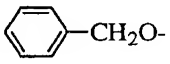
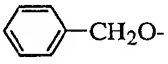
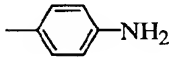
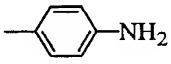


Table 30

Ex. No.	A^1	R^1	Physicochemical properties
334	H		m.p. 203-205°C
335			m.p. 232-234°C (decomp.)
336			m.p. 241-243°C
337*	HO-		m.p. 222-224°C (decomp.)

*: monohydrochloride

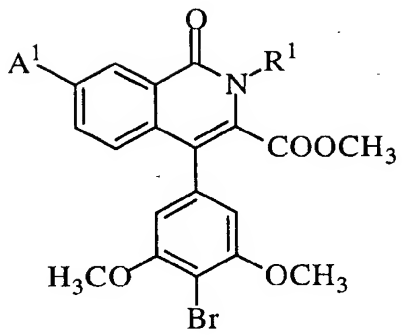
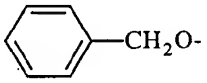
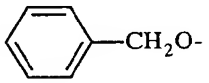
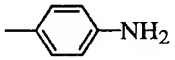
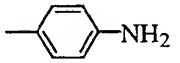


Table 31

Ex. No.	A^1	R^1	Physicochemical properties
338			m.p. 143-145°C
339*			m.p. 168-171°C (decomp.)
340 (1) (2)*	HO–		(1)m.p. >250°C (2)m.p. 247-249°C (decomp.)

*: monohydrochloride

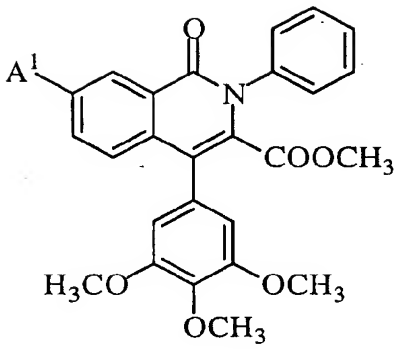
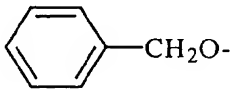
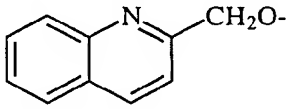
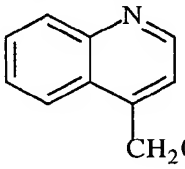
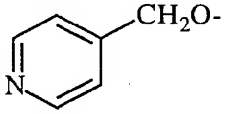
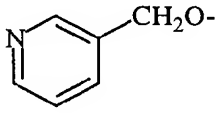
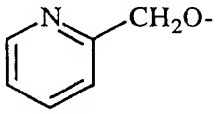


Table 32

Ex. No.	A^1	Physicochemical properties
341		m.p. 148-149°C
342	HO-	m.p. 236-238°C
343*		m.p. 209-212°C (decomp.)
344*		m.p. 171-172°C (decomp.)
345*		m.p. 228-230°C (decomp.)
346*		m.p. 151-153°C (decomp.)
347*		m.p. 126-128°C (decomp.)

*: monohydrochloride

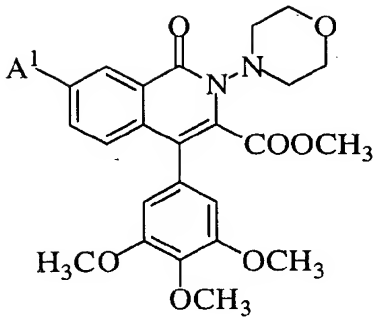
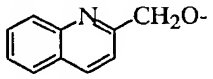


Table 33

Ex. No.	A^1	Physicochemical properties
348*		m.p. 142-147°C (decomp.)

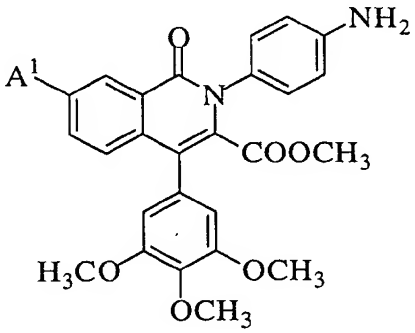
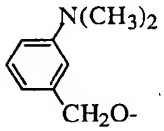
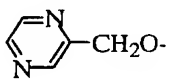
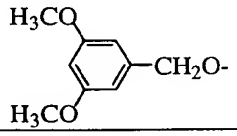
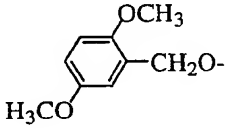


Table 34

Ex. No.	A^1	Physicochemical properties
349**		m.p. 170-173°C (decomp.)
350**		m.p. 188-192°C (decomp.)
351*		m.p. 208-213°C (decomp.)
352*		m.p. 121-123°C (decomp.)

*: monohydrochloride
**: dihydrochloride

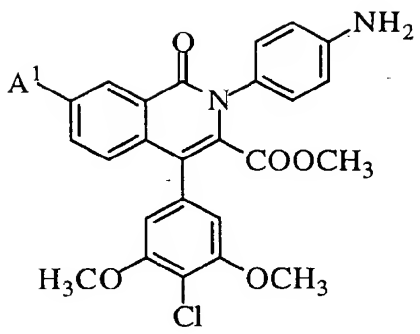
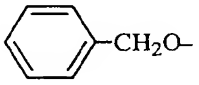
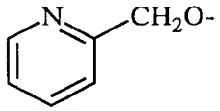
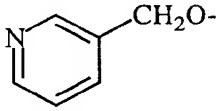
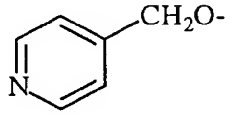
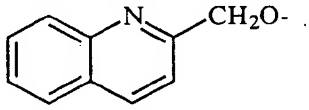


Table 35

Ex. No.	A^1	Physicochemical properties
353*		m.p. 203-205°C (decomp.)
354	HO-	m.p. >250°C
355**		m.p. 210-213°C (decomp.)
356**		m.p. 213-216°C (decomp.)
357**		m.p. 222-225°C (decomp.)
358**		m.p. 210-215°C (decomp.)

*: monohydrochloride
**: dihydrochloride

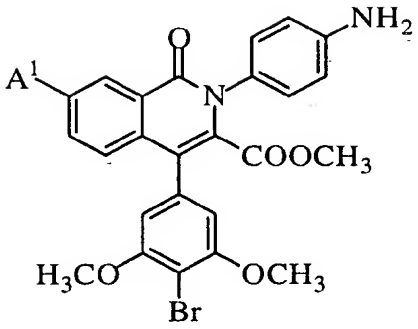
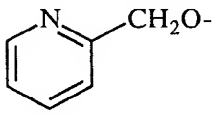
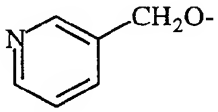
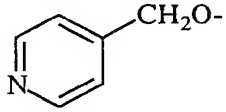
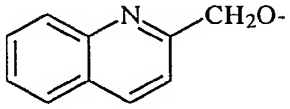
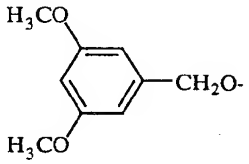
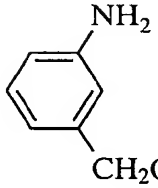


Table 36

Ex. No.	A^1	Physicochemical properties
359**		m.p. 194-197°C (decomp.)
360**		m.p. 204-206°C (decomp.)
361**		m.p. 205-208°C (decomp.)
362**		m.p. 235-239°C (decomp.)
363*		m.p. 235-238°C (decomp.)
364**		m.p. 208-210°C (decomp.)

*: monohydrochloride
**: dihydrochloride

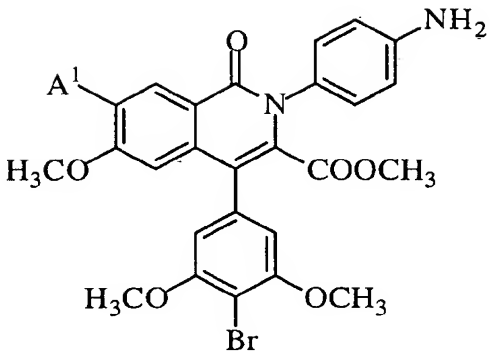
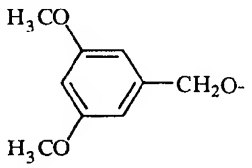
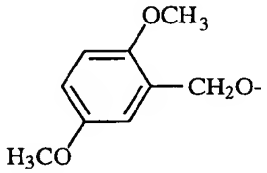
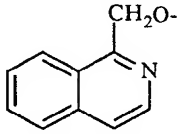


Table 37

Ex. No.	A^1	Physicochemical properties
365*		m.p. 184-187°C (decomp.)
366*		m.p. 178-182°C (decomp.)
367*	$NCCH_2O$-	m.p. 172-175°C (decomp.)
368**		m.p. 215-218°C (decomp.)

*: monohydrochloride
**: dihydrochloride

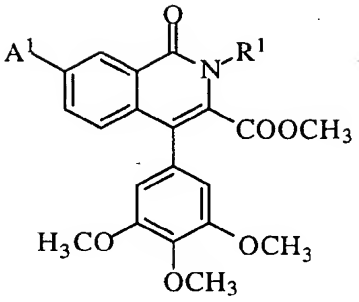
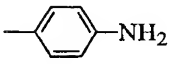
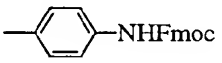
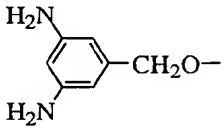
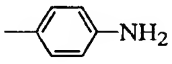
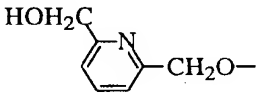
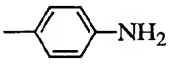
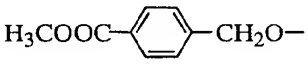
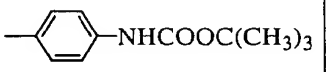
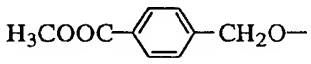
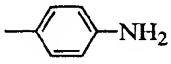
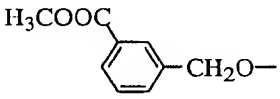
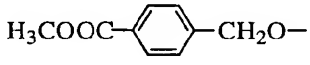
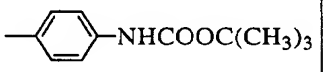
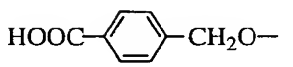
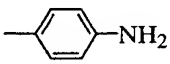


Table 38

Ex. No.	A^1	R^1	Physicochemical properties
369	HO–		m.p. 149-151°C
370	HO–		m.p. >250°C
371***			m.p. 190-200°C (decomp.)
372**			m.p. 185-190°C (decomp.)
373(1)			m.p. 148-150°C
373(2)*			m.p. 221-224°C (decomp.)
374			m.p. 206-209°C
375(1)			m.p. 216-218°C (decomp.)
375(2)*			m.p. 237-240°C (decomp.)

*: monohydrochloride **: dihydrochloride
***: trihydrochloride Fmoc: 9-fluorenylmethyloxycarbonyl group

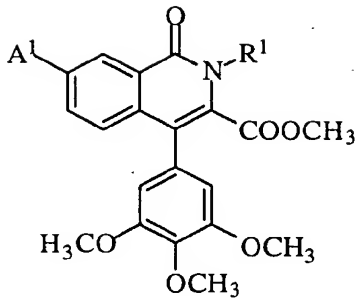
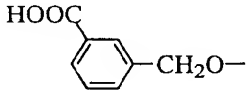
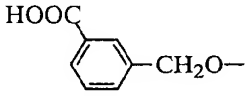
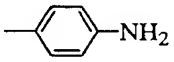
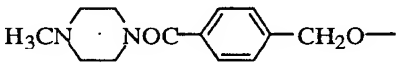
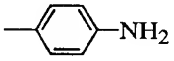
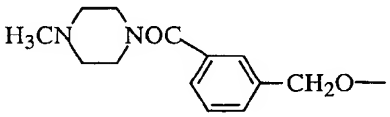
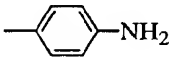
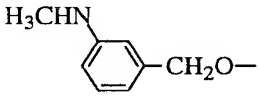
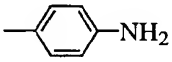
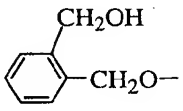
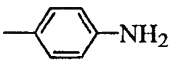
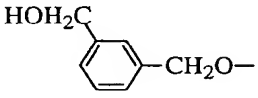
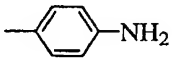
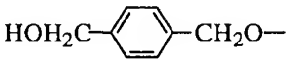
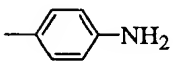


Table 39

Ex. No.	A^1	R^1	Physicochemical properties
376(1)			m.p. 150-153°C
376(2)*			m.p. 164-165°C (decomp.)
377**			m.p. 212-215°C (decomp.)
378**			m.p. 215-218°C (decomp.)
379**			m.p. 215-218°C (decomp.)
380*			m.p. >230°C
381*			m.p. 126-130°C (decomp.)
382*			m.p. 133-138°C (decomp.)

*: monohydrochloride
**: dihydrochloride

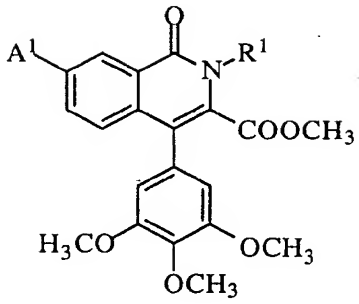
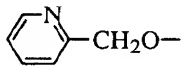
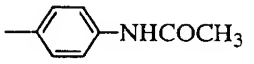
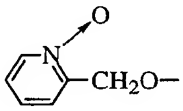
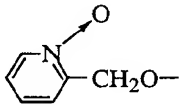
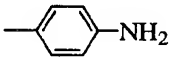
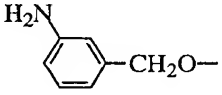
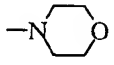
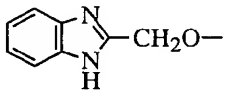
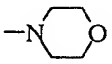
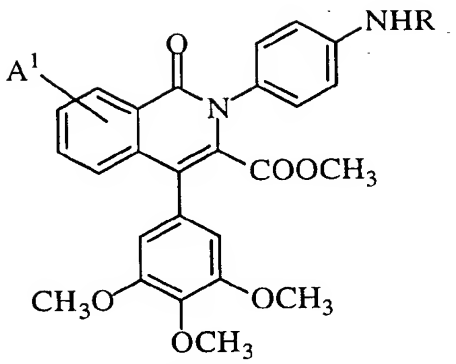


Table 40

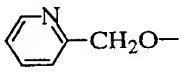
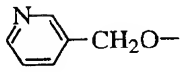
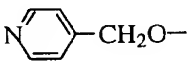
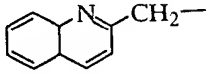
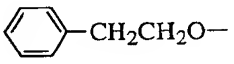
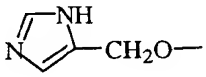
Ex. No.	A^1	R^1	Physicochemical properties
383			m.p. 194-198°C
384(1)			m.p. 190-195°C (decomp.)
384(2)			m.p. 190-195°C (decomp.)
385*			m.p. 226-228°C (decomp.)
386			m.p. 232-234°C

*: monohydrochloride



(R=H in Examples 384-393, and R=SO_2CH_3 in Example 394)

Table 41

Ex. No.	A^1	Substituted position of A^1	Physicochemical properties
387	HO–	8	m.p. 233-235°C
388**		8	m.p. 201-204°C (decomp.)
389**		8	m.p. 222-224°C (decomp.)
390**		8	m.p. 239-244°C (decomp.)
391**		8	m.p. 220-224°C (decomp.)
392*		8	m.p. 224-228°C (decomp.)
393**		7	m.p. 211-215°C (decomp.)
394		7	m.p. 135-137°C

*: monohydrochloride
**: dihydrochloride

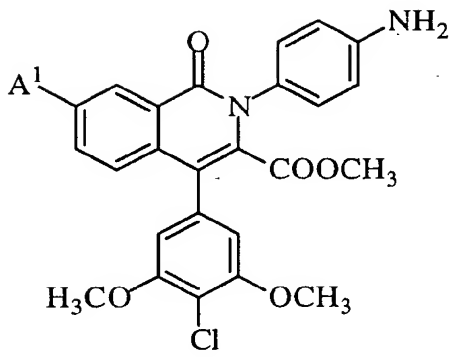
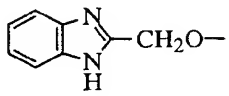
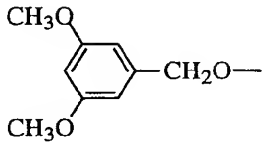
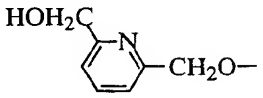
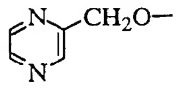
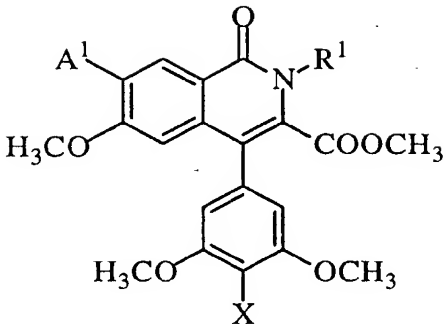


Table 42

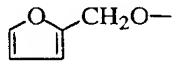
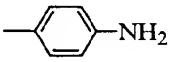
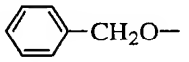
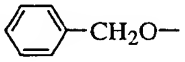
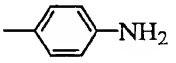
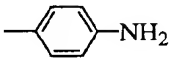
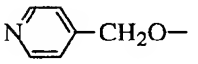
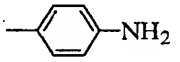
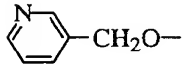
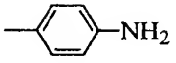
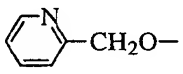
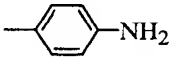
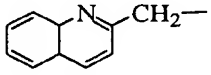
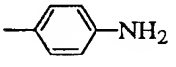
Ex. No.	A^1	Physicochemical properties
395**		m.p. 248-252°C (decomp.)
396*		m.p. 234-238°C (decomp.)
397**		m.p. 226-230°C (decomp.)
398**		m.p. 201-205°C (decomp.)

*: monohydrochloride
**: dihydrochloride



(X=Br in Example 399, and X=CH_3 in Examples 400-407)

Table 43

Ex. No.	A^1	R^1	Physicochemical properties
399*			m.p. 185-188°C (decomp.)
400			m.p. 164-165°C
401*			m.p. 205-208°C (decomp.)
402	HO–		m.p. >250°C
403*	HO–		m.p. 235-240°C (decomp.)
404**			m.p. 210-213°C (decomp.)
405**			m.p. 212-217°C (decomp.)
406**			m.p. 206-209°C (decomp.)
407**			m.p. 198-201°C (decomp.)

*: monohydrochloride
**: dihydrochloride

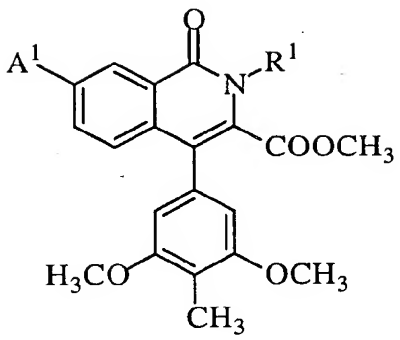
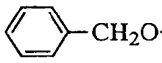
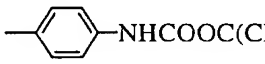
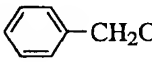
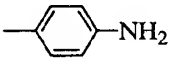
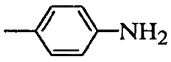
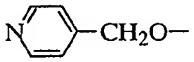
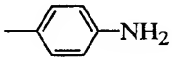
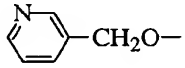
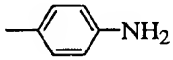
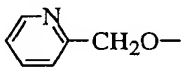
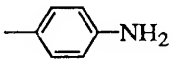


Table 44

Ex. No.	A^1	R^1	Physicochemical properties
408			m.p. 132-134°C
409*			m.p. 188-191°C (decomp.)
410	HO–		m.p. 234-235°C
411*	HO–		m.p. 245-249°C (decomp.)
412**			m.p. 229-234°C (decomp.)
413**			m.p. 200-205°C (decomp.)
414**			m.p. 203-206°C (decomp.)

*: monohydrochloride
**: dihydrochloride

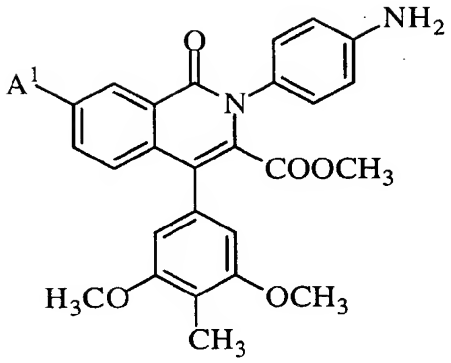
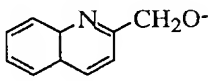
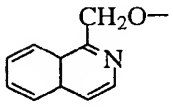
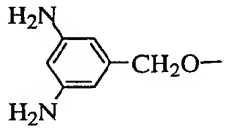
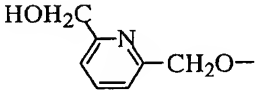
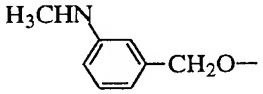
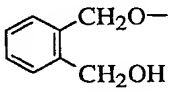
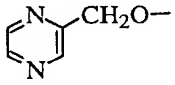


Table 45

Ex. No.	A^1	Physicochemical properties
415**		m.p. 205-209°C (decomp.)
416**		m.p. 194-198°C (decomp.)
417***		m.p. 190-200°C (decomp.)
418**		m.p. 185-189°C (decomp.)
419**		m.p. 198-202°C (decomp.)
420*		m.p. 237-243°C (decomp.)
421**		m.p. 168-171°C (decomp.)

*: monohydrochloride
**: dihydrochloride
***: trihydrochloride

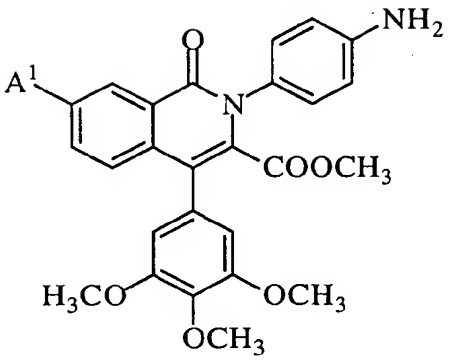
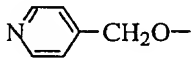
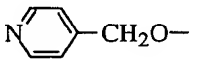
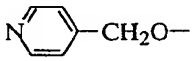
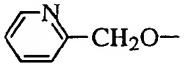
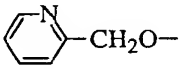


Table 46

Ex. No.	A^1	Physicochemical properties
422 (1)		m.p. 230-231°C
422 (2)		monosulfate m.p. 232-236°C (decomp.)
423		dimethanesulfonate m.p. >250°C
424		monosulfate m.p. 221-223°C (decomp.)
425		dimethanesulfonate m.p. 190-193°C

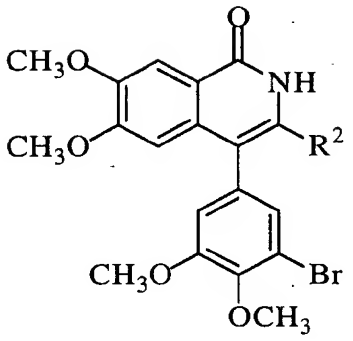


Table 47

Ex. No.	R^2	Physicochemical properties
426	–COOH	m.p. >220°C
427	$-COOCH_3$	m.p. 204-206°C

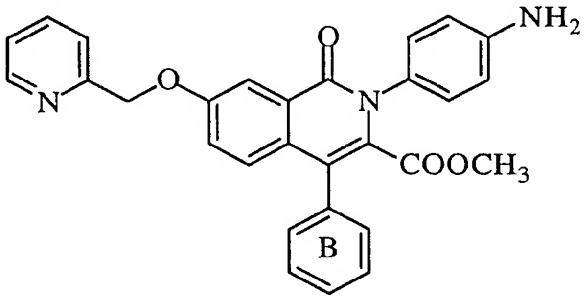
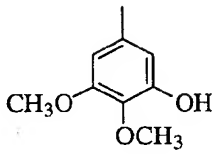
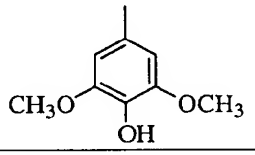


Table 48

Ex. No.	Ring B	Physicochemical properties
428 (3)**		m.p. 196-199°C (decomp.)
429		m.p. 202-205°C

**: dihydrochloride

Example 1

7-Benzyloxy-6-methoxy-4-(3,4,5-trimethoxyphenyl)isocoumarin-3-carboxylic acid (5.0 g) and 4-aminomorpholine (6.2 g) are dissolved in 1,3-dimethyl-2-imidazolidinone (20 ml), and the mixture is heated at 100°C with stirring overnight. To the reaction mixture are added chloroform and water. The chloroform layer is separated, washed, dried, and concentrated under reduced pressure to give 7-benzyloxy-3-carboxy-6-methoxy-2-morpholino-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone. The product thus obtained is dissolved in dimethylformamide (15 ml), and thereto are added potassium carbonate (2.1 g) and methyl iodide (1.27 ml). The mixture is stirred at room temperature for 30 minutes, and thereto are added ethyl acetate and water. The ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure. The residue is crystallized from diethyl ether to give 7-benzyloxy-6-methoxy-3-methoxycarbonyl-2-morpholino-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (3.4 g) as listed in Table 1.

Example 2

To the compound obtained in Example 1 (2.8 g) are added methanol (100 ml), dimethylformamide (100 ml) and palladium-carbon (100 mg), and the mixture is stirred under hydrogen atmosphere (1 atm) at room temperature for 1.5 hour. The catalyst is removed by filtration, and the filtrate is concentrated. The precipitated crystals are collected by filtration, and washed with diethyl ether to give 7-hydroxy-6-methoxy-3-methoxycarbonyl-2-morpholino-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (2.26 g) as listed in Table 1.

Example 3

To a solution of the compound obtained in Example 2 (300 mg) in

dimethylformamide (3 ml) are added 2-picolyl chloride hydrochloride (118 mg) and potassium carbonate (182 mg), and the mixture is stirred at 50°C overnight. To the mixture are added ethyl acetate and water. The ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure. The residue (chemical name; 6-methoxy-3-methoxycarbonyl-2-morpholino-7-(2-pyridyl-methyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone) is dissolved in ethyl acetate, and thereto is added a 4M solution of hydrogen chloride in ethyl acetate (150 μl). The mixture is stirred at room temperature for 30 minutes. The precipitated crystals are collected by filtration, and washed with ethyl acetate to give 6-methoxy-3-methoxycarbonyl-2-morpholino-7-(2-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (279 mg) as listed in Table 1.

Example 4

To 7-benzyloxy-3-hydroxy-6-methoxy-4-(3,4,5-trimethoxyphenyl)-3,4-dihydroisocoumarin-3-carboxylic acid (the compound obtained in Reference Example 71) (12.8 g) are added 1,3-dimethyl-2-imidazolidinone (60 ml), N-methylmorpholine (4.15 ml) and N-tert-butoxycarbonyl-p-phenylenediamine (6.78 g), and the mixture is heated at 80°C with stirring overnight. The reaction mixture is cooled to room temperature, and thereto are added a saturated aqueous citric acid solution and ethyl acetate. The ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure to give 7-benzyloxy-2-[4-(tert-butoxycarbonylamino)phenyl]-3-carboxy-6-methoxy-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoqunolinone. The product is dissolved in dimethylformamide (60 ml), and thereto are added potassium carbonate (4.14 g) and methyl iodide (1.87 ml) under ice-cooling, and the mixture is stirred at room

temperature overnight. To the mixture are added water and ethyl acetate. The ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure. The residue is crystallized from diethyl ether to give 7-benzyloxy-2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (14.2 g) as listed in Table 2.

Example 5

To a solution of the compound obtained in Example 4 (17.0 g) in a mixture of tetrahydrofuran (150 ml) and methanol (100 ml) is added palladium-carbon (1.0 g) under nitrogen atmosphere, and the mixture is subjected to catalytic reduction (3 atms) for one hour. The palladium-carbon is removed by filtration, and the filtrate is concentrated under reduced pressure. The residue is crystallized from diethyl ether to give 2-[4-(tert-butoxycarbonylamino)phenyl]-7-hydroxy-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (13.3 g) as listed in Table 2.

Example 6

(1) The compound obtained in Example 5 (200 mg) is dissolved in dimethylformamide (20 ml), and thereto are added potassium carbonate (92 mg), and 2-picolyl chloride hydrochloride (55 mg). The mixture is stirred at 60°C overnight, and thereto are added water and ethyl acetate. The ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; hexane:ethyl acetate = 1:2) to give 2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-7-(2-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (207 mg).

(2) The compound thus obtained is dissolved in chloroform (5 ml), and

thereto is added a 4M solution of hydrogen chloride in ethyl acetate (8 ml), and the mixture is stirred at room temperature for 5 minutes. To the resulting suspension is added methanol (1 ml), and the mixture is stirred overnight. To the mixture is added diethyl ether, and the precipitated crystals are collected by filtration to give 2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(2-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (180 mg) as listed in Table 2.

Example 7

(1) The compound obtained in Example 5 (250 mg), 3-hydroxymethylquinoline (98 mg) and triphenylphosphine (215 mg) are dissolved in THF (10 ml), and thereto is added diethyl azodicarboxylate (97.3 μl). The mixture is stirred at room temperature for 10 minutes, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; hexane:ethyl acetate = 1:2) to give 2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-7-(3-quinolylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone.

(2) The compound thus obtained is dissolved in chloroform (3 ml), and thereto is added a 4M solution of hydrogen chloride in ethyl acetate (5 ml), and the mixture is stirred at room temperature for 5 minutes. To the resulting suspension is added methanol (1 ml), and the mixture is stirred overnight. To the reaction mixture is added diethyl ether, and the precipitated crystals are collected by filtration to give 2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(3-quinolylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (140 mg) as listed in Table 2.

Example 8

(1) The compound obtained in Example 5 (10.0 g) is dissolved in chloroform (20 ml), and thereto are added a 4M solution of hydrogen chloride in ethyl acetate (60 ml). The mixture is stirred at room temperature overnight. The resulting suspension is neutralized with 2M aqueous sodium hydroxide solution (120 ml) under ice-cooling, and the mixture is extracted with ethyl acetate. The ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure. The residue is dissolved in a small amount of ethyl acetate, and crystallized from diethyl ether to give 2-(4-aminophenyl)-7-hydroxy-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (5.47 g).

(2) The compound thus obtained (5.47 g) is dissolved in a mixture of acetonitrile (50 ml) and 1,3-dimethyl-2-imidazolidinone (5 ml), and thereto is added 9-fluorenylmethyl chloroformate (2.8 g). The mixture is stirred at room temperature for 10 minutes. To the reaction mixture are added water and ethyl acetate. The ethyl acetate layer is washed, dried, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; hexane:ethyl acetate = 1:2) to give 2-[4-(9-fluorenylmethyloxy-carbonylamino)phenyl]-7-hydroxy-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (3.38 g) as listed in Table 2.

Example 9

(1) The compound obtained in Example 8-(2) (418 mg), 2-hydroxymethyl-thiophene (97.6 μl), and triphenylphosphine (270 mg) are dissolved in tetrahydrofuran (10 ml), and thereto is added diethyl azodicarboxylate (162 μl). The mixture is stirred at room temperature for 10 minutes, and after the reaction is complete, the mixture is concentrated under reduced pressure. The residue is

purified by silica gel column chromatography (solvent; hexane:ethyl acetate = 1:1) to give 2-[4-(9-fluorenylmethyloxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-7-(2-thienylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone.

(2) The compound thus obtained is dissolved in dimethylformamide (10 ml), and thereto is added piperidine (50 µl), and the mixture is stirred at room temperature overnight. To the mixture are added water and ethyl acetate. The ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; hexane:ethyl acetate = 1:4) to give 2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(2-thienylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (187 mg), m.p. 205-206°C.

(3) The compound thus obtained (155 mg) is dissolved in chloroform (5 ml), and thereto is added a 4M solution of hydrogen chloride in ethyl acetate (66 µl), and the mixture is stirred at room temperature for 30 minutes. To the mixture is diethyl ether, and the precipitated crystals are collected by filtration to give 2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(2-thienylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (76 mg) as listed in Table 2.

Example 10

(1) 6,7-Dimethoxy-4-(3,4,5-trimethoxyphenyl)isocoumarin-3-carboxylic acid (= the compound obtained in Reference Example 50) (2.0 g) and aniline (2.61 g) are dissolved in 1-methyl-2-pyrrolidinone (5 ml), and the mixture is heated with stirring at 120°C overnight. To the reaction mixture are added ethyl acetate and water. The ethyl acetate layer is separated, washed, dried, and

concentrated under reduced pressure to give 3-carboxy-2-phenyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (1.98 g).

(2) The compound thus obtained (1.97 g) is dissolved in dimethylformamide (20 ml), and thereto are added potassium carbonate (1.16 g) and methyl iodide (1.59 g). The mixture is stirred at room temperature overnight, and thereto are added chloroform and water. The chloroform layer is separated, washed, dried, concentrated under reduced pressure, and the residue is crystallized from ethyl acetate to give 3-methoxycarbonyl-2-phenyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (1.69 g) as listed in Table 3.

Examples 11-13, 11a-13a

The corresponding starting compounds are treated in the same manner as in Example 10-(2) to give the following compounds as listed in Table 3.

3-ethoxycarbonyl-2-phenyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 11);

3-benzyloxycarbonyl-2-phenyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 12);

3-n-butoxycarbonyl-2-phenyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 13);

3-ethoxycarbonyl-4-(4-ethoxy-3,5-dimethoxyphenyl)-2-phenyl-1(2H)-isoquinolinone (Example 11a);

3-benzyloxycarbonyl-4-(4-benzyloxy-3,5-dimethoxyphenyl)-2-phenyl-1(2H)-isoquinolinone (Example 12a);

3-n-butoxycarbonyl-4-(4-n-butoxy-3,5-dimethoxyphenyl)-2-phenyl-1(2H)-isoquinolinone (Example 13a);

Examples 14-15

4-(3,4,5-Trimethoxyphenyl)isocoumarin-3-carboxylic acid (the compound obtained in Reference Example 51) and the corresponding starting compounds are treated in the same manner as in Example 1 to give the following compounds as listed in Table 4.

2-(2-chlorophenyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 14);

3-methoxycarbonyl-2-(2-naphthyl)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 15);

Examples 16-18

The compound obtained in Reference Example 51 and the corresponding starting compounds are treated in the same manner as in Example 4 to give the following compounds as listed in Table 4.

2-(4-n-butylphenyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 16);

2-[3,5-bis(methoxycarbonyl)phenyl]-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 17);

3-methoxycarbonyl-2-(3-nitrophenyl)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 18);

Example 19

The compound obtained in Reference Example 51 and the corresponding starting compounds are treated in the same manner as in Example 1 to give 2-dimethylamino-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 4.

Example 20

The compound obtained in Reference Example 51 and the corresponding

starting compounds are treated in the same manner as in Example 4 to give 3-methoxycarbonyl-2-(4-methoxycarbonylphenyl)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 4.

Example 21

(1) To the compound obtained in Example 20 (1.51 g) are added methanol (150 ml) and 1M aqueous sodium hydroxide solution (3 ml), and the mixture is stirred at 60°C overnight. To the reaction solution is further added 1M aqueous sodium hydroxide solution (1.5 ml) which is divided to two portions, and the mixture is refluxed for 12 hours. The reaction mixture is allowed to stand for cooling, and thereto are added water and ethyl acetate. The aqueous layer is separated, and acidified with hydrochloric acid, and further extracted with ethyl acetate. The ethyl acetate layers are combined, washed, dried, and concentrated under reduced pressure. The residue is crystallized from diethyl ether to give 2-(4-carboxyphenyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (245 mg) as listed in Table 4.

(2) The compound thus obtained (245 mg) is dissolved with heating in 1M aqueous sodium hydroxide solution (0.50 ml). Water is removed by under reduced pressure from the mixture, and thereto is added diethyl ether. The precipitated crystals are collected by filtration to give 2-(4-carboxyphenyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone sodium salt (245 mg) as listed in Table 4.

Example 22

A solution of the compound obtained in Example 21 (200 mg), 1-hydroxybenzotriazole (69 mg) and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (86 mg) in methylene chloride (10 ml) is stirred at

room temperature for 30 minutes. To the mixture is added a solution of morpholine (71 mg) in methylene chloride (2 ml), and the mixture is stirred at room temperature overnight. After the reaction is complete, to the mixture are added water and ethyl acetate. The ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure. The residue is crystallized from diethyl ether to give 3-methoxycarbonyl-2-[4-(morpholinocarbonyl)phenyl]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (210 mg) as listed in Table 4.

Example 23

The compound obtained in Example 21 and tert-butyl carbazate are treated in the same manner as in Example 22 to give 2-[4-(tert-butoxycarbonyl-hydrazinocarbonyl)phenyl]-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 4.

Example 24

The compound obtained in Example 23 is dissolved in dioxane (2 ml), and thereto is added a 4M solution of hydrogen chloride in dioxane (5 ml), and the mixture is stirred at room temperature. To the reaction mixture is further added a 4M solution of hydrogen chloride in dioxane (5 ml), and the mixture is stirred for three hours. The reaction mixture is concentrated under reduced pressure, and the residue is purified by silica gel column chromatography (solvent; chloroform:methanol = 30:1) to give 3-methoxycarbonyl-2-[4-(hydrazinocarbonyl)phenyl]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 4.

Examples 25-26

A solution of 3-hydroxy-4-(3,4,5-trimethoxyphenyl)-3,4-dihydro-isocoumarin-3-carboxylic acid (the compound obtained in Reference Example

75) (1.87 g), 1,4-diaminocyclohexane (1.14 g) and N-methylmorpholine (0.55 ml) in 1,3-dimethyl-2-imidazolidinone (10 ml) is heated with stirring at 100°C for 30 minutes. The reaction mixture is cooled, and acidified with hydrochloric acid, and thereto is added ethyl acetate (20 ml). The pH value of the aqueous layer is adjusted to pH 9 with potassium carbonate, and thereto are added methanol (30 ml), tetrahydrofuran (100 ml) and di-tert-butyl dicarbonate (5.44 g), and the mixture is stirred at room temperature for 6 hours. The reaction mixture is acidified with 10 % aqueous citric acid solution, and extracted with ethyl acetate. The extract is washed, dried, and concentrated under reduced pressure. To the residue are added methanol (50 ml), ethyl acetate (100 ml) and a 2M solution of trimethylsilyldiazomethane in hexane (2.5 ml), and the mixture is stirred at room temperature for one hour. The reaction mixture is concentrated under reduced pressure, and the residue is purified by silica gel column chromatography (solvent; chloroform:ethyl acetate = 10:1) to give the following compounds as listed in Table 4.

2-[cis-4-(tert-butoxycarbonylamino)cyclohexyl]-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 25);

2-[trans-4-(tert-butoxycarbonylamino)cyclohexyl]-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 26);

Examples 27-28

The compounds obtained in Examples 25-26 are treated in the same manner as in Example 24 to give the following compounds as listed in Table 4.

2-(cis-4-aminocyclohexyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 27);

2-(trans-4-aminocyclohexyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxy-

phenyl)-1(2H)-isoquinolinone hydrochloride (Example 28);

Example 29

3-Hydroxy-4-(3,4,5-trimethoxyphenyl)-3,4-dihydroisocoumarin-3-carboxylic acid (the compound obtained in Reference Example 75) and the corresponding starting compounds are treated in the same manner as in Example 25 to give 2-[3-(N-tert-butoxycarbonyl)pyrrolidinyl]-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 4.

Example 30

The compound obtained in Example 29 is treated in the same manner as in Example 24 to give 3-methoxycarbonyl-2-(3-pyrrolidinyl)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 4.

Example 31

To 3-hydroxy-4-(3,4,5-trimethoxyphenyl)-3,4-dihydroisocoumarin-3-carboxylic acid (the compound obtained in Reference Example 75) (500 mg) are added 1,3-dimethyl-2-imidazolidinone (5 ml) and 4-aminobenzenesulfonamide (920 mg), and the mixture is heated with stirring at 90°C with stirring for three hours, and then further heated with stirring at 120°C overnight. The reaction mixture is allowed to stand for cooling, and thereto are added 5 % aqueous potassium carbonate solution (20 ml) and ethyl acetate (10 ml). The aqueous layer is separated, acidified with 10 % aqueous citric acid solution, and extracted with ethyl acetate. The ethyl acetate layers are combined, washed, dried, and concentrated under reduced pressure to give 2-(4-sulfamoylphenyl)-3-carboxy-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone, which is dissolved in a mixture of methanol (5 ml) and ethyl acetate (20 ml). To the mixture is added a 2M solution of trimethylsilyldiazomethane in hexane (0.67 ml), and the

mixture is stirred at room temperature for 30 minutes. The mixture is concentrated under reduced pressure, and the residue is purified by silica gel column chromatography (solvent; chloroform:acetone = 9:1) to give 2-(4-sulfamoylphenyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (88 mg) as listed in Table 4.

Example 32

The compound obtained in Reference Example 75 and the corresponding starting compounds are treated in the same manner in Example 4 or 31 to give 3-methoxycarbonyl-2-[4-(N-tert-butoxycarbonyl)piperidyl]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 4.

Example 33

(1) The compound obtained in Example 32 is treated in the same manner as in Example 24 to give 3-methoxycarbonyl-2-(4-piperidyl)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride.

(2) To the compound thus obtained (1.10 g) are added 10 % aqueous potassium carbonate solution and ethyl acetate. The ethyl acetate layer is separated, washed with water, dried, and concentrated under reduced pressure to give 3-methoxycarbonyl-2-(4-piperidyl)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 4.

Example 34

The compound obtained in Reference Example 75 and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give 2-[3-amino-5-(methoxycarbonyl)phenyl]-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 4.

Example 35

The compound obtained in Example 34 is treated in the same manner as in Example 21 to give 2-(3-amino-5-carboxyphenyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 4.

Examples 36-38

The compound obtained in Reference Example 51 and the corresponding starting compounds are treated in the same manner as in Example 1 to give the following compounds as listed in Table 4.

2-(2-indanyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 36);

2-(5-indanyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 37);

3-methoxycarbonyl-2-[(N-methyl-4-piperidyl)methyl]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 38);

Example 39

(1) 4-(3,4,5-Trimethoxyphenyl)isocoumarin-3-carboxylic acid (the compound obtained in Reference Example 51) (1.42 g) and N-acetyl-p-phenylenediamine (1.80 g) are dissolved in 1,3-dimethyl-2-imidazolidinone (3 ml), and the mixture is heated with stirring at 130°C for 4 hours. The pH value of the reaction mixture is adjusted to pH 2 with 0.1M hydrochloric acid under ice-cooling. The mixture is stirred under ice-cooling, and the precipitated crystals are collected by filtration. The crystals are washed successively with water and chloroform to give 2-(4-acetylaminophenyl)-3-carboxy-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (1.02 g).

(2) The compound thus obtained (0.50 g) is dissolved in a mixture of methanol (10 ml) and chloroform (10 ml), and thereto is added a 2M solution of

trimethylsilyldiazomethane in hexane (2 ml). The mixture is stirred at room temperature for three hours, and concentrated under reduced pressure. To the residue are added water and chloroform. The chloroform layer is separated, washed with aqueous sodium hydrogen carbonate solution and a saturated aqueous sodium chloride solution, dried, and concentrated under reduced pressure. The residue is crystallized from diethyl ether to give 3-methoxycarbonyl-2-(4-acetylaminophenyl)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (440 mg) as listed in Table 4.

Example 40

The compound obtained in Example 39-(1) (0.50 g) is added to 2M hydrochloric acid (10 ml), and the mixture is heated under reflux for 12 hours. To the reaction mixture are added 2M aqueous sodium hydroxide solution under ice-cooling, and the pH value of the mixture is adjusted to pH 6-7. The precipitated crystals are collected by filtration, and washed with water to give 2-(4-aminophenyl)-3-carboxy-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (0.40 g), which is further treated in the same manner as in Example 39-(2) to give 2-(4-aminophenyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (0.30 g). The compound thus obtained is dissolved in chloroform, and thereto is added a 4M solution of hydrogen chloride in dioxane (0.16 ml). The mixture is concentrated, and the residue is crystallized from ethyl acetate to give 2-(4-aminophenyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (0.28 g) as listed in Table 4.

Examples 41-42

The compound obtained in Reference Example 51 and the corresponding starting compounds are treated in the same manner as in Example 1 or 39 to give

the following compounds as listed in Table 4.

2-(3,4-dimethoxyphenyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 41);

2-(3,5-dimethoxyphenyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 42);

Example 43

(1) The compound obtained in Reference Example 51 and the corresponding starting compounds are treated in the same manner as in Example 39 to give 2-(3-amino-4-methoxyphenyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone.

(2) The compound thus obtained is dissolved in ethyl acetate, and thereto is added a 4M solution of hydrogen chloride in dioxane. The mixture is concentrated under reduced pressure, crystallized from ethyl acetate to give 2-(3-amino-4-methoxyphenyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 4.

Examples 44-45

The compound obtained in Reference Example 75 and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give the following compounds as listed in Table 4.

3-methoxycarbonyl-2-[3-(2-oxotetrahydrofuryl)]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 44);

3-methoxycarbonyl-2-[3-(2-oxopyrrolidinyl)]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 45);

Example 46

(1) The compound obtained in Reference Example 75 and the

corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give 2-(6-indolinyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone.

(2) The compound thus obtained is treated in the same manner as in Example 43-(2) to give 2-(6-indolinyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 4.

Examples 47-50

The compound obtained in Reference Example 75 and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give the following compounds as listed in Table 4.

2-cyclopropyl-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 47);

2-(trans-4-hydroxycyclohexyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 48);

2-ethyl-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 49);

2-[4-(1-benzyl)piperidyl]-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 50);

Examples 51-53

The compound obtained in Reference Example 51 and the corresponding starting compounds are treated in the same manner as in Example 1 or 39 to give the following compounds as listed in Table 4.

3-methoxycarbonyl-2-(3-trifluoromethylphenyl)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 51);

2-(5(1H)-indazolyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-

1(2H)-isoquinolinone (Example 52);

3-methoxycarbonyl-2-piperidino-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 53);

Example 54

The compound obtained in Reference Example 75 and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give 2-(3-hydroxy-n-propyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 4.

Example 55

(1) The compound obtained in Reference Example 75 and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give 2-[1-(4-benzyloxycarbonyl)piperazinyl]-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone, which is used in the subsequent reaction without further purification.

(2) The compound thus obtained (260 mg) is dissolved in a 25 % solution of hydrogen bromide in acetic acid (3 ml), and the mixture is stirred at room temperature for 30 minutes. The reaction mixture is poured into a saturated aqueous sodium hydrogen carbonate solution, and the mixture is extracted with ethyl acetate. The extract is washed, dried, and concentrated under reduced pressure. To a solution of the residue in chloroform is added a 4M solution of hydrogen chloride in ethyl acetate (75 μl), and the precipitated crystals are collected by filtration to give 3-methoxycarbonyl-2-(1-piperazinyl)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (95 mg) as listed in Table 4.

Examples 56-58

The compound obtained in Reference Example 75 and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give the following compounds as listed in Table 4.

3-methoxycarbonyl-2-morpholino-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 56);

3-methoxycarbonyl-2-(3-pyridyl)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 57);

2-[4-(benzyloxycarbonylaminomethyl)phenyl]-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 58);

Example 59

The compound obtained in Example 58 (300 mg) is dissolved in a 25 % solution of hydrogen bromide in acetic acid (10 ml), and the mixture is stirred at room temperature overnight. The precipitated crystals are collected by filtration, washed, and thereto are added chloroform and aqueous sodium hydrogen carbonate solution. The chloroform layer is washed, dried, and concentrated. The residue is dissolved in ethyl acetate (3 ml), and thereto is added a 4M solution of hydrogen chloride in ethyl acetate (150 µl). The precipitated crystals are collected by filtration to give 2-(4-aminomethylphenyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (215 mg) as listed in Table 4.

Examples 60-61

The compound obtained in Reference Example 75 and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give the following compounds as listed in Table 4.

3-methoxycarbonyl-2-[(6-methyl-2-pyridinon-3-yl)methyl]-4-(3,4,5-

trimethoxyphenyl)-1(2H)-isoquinolinone (Example 60);

3-methoxycarbonyl-2-(3,4-methylenedioxybenzyl)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 61);

Examples 62-63

The compound obtained in Reference Example 75 and the corresponding starting compounds are treated in the same manner as in Example 46 to give the following compounds as listed in Table 4.

2-(3-dimethylaminophenyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 62);

3-methoxycarbonyl-2-[3-(6-methoxy)pyridyl]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 63);

Example 64

The compound obtained in Reference Example 75 and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give 3-methoxycarbonyl-2-(3-methoxycarbonylphenyl)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 4.

Example 65

The compound obtained in Example 64 is treated in the same manner as in Example 21 to give 2-(3-carboxyphenyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 4.

Example 66

The compound obtained in Reference Example 51 and the corresponding starting compounds are treated in the same manner as in Example 10-(1) to give 2-(tert-butoxycarbonylamino)-3-carboxy-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 5.

Example 67

The compound obtained in Example 66 (1.0 g), dimethylaminopyridine (26 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (448 mg) are dissolved in a mixture of methylene chloride (20 ml) and methanol (340 ml). The mixture is stirred at room temperature for 10 minutes, and thereto are added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (41 mg) and dimethylaminopyridine (26 mg), and the mixture is stirred at room temperature overnight. To the reaction mixture are added water and ethyl acetate, and the ethyl acetate layer is washed, dried, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; hexane:ethyl acetate = 2:1) to give 2-(tert-butoxycarbonylamino)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (438 mg) as listed in Table 6.

Example 68

To the compound obtained in Example 67 (200 mg) is added a 4M solution of hydrogen chloride in ethyl acetate (10 ml) and the mixture is allowed to stand at room temperature for one hour. The reaction mixture is concentrated under reduced pressure, and to the residue is added ethyl acetate. The mixture is washed with a saturated aqueous sodium hydrogen carbonate solution, dried, and concentrated under reduced pressure to give 2-amino-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (146 mg) as listed in Table 6.

Example 69

To a solution of the compound obtained in Example 68 (200 mg) and pyridine (120 mg) in tetrahydrofuran (15 ml) is added dropwise a solution of acetyl chloride (61.3 mg) in tetrahydrofuran (5 ml) under ice-cooling, and the

mixture is stirred under ice-cooling for one hour, and further stirred at room temperature overnight. To the reaction mixture are added ethyl acetate and water, and the ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure. The residue is crystallized from a mixture of hexane-diethyl ether to give 2-acetylamino-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (116 mg) as listed in Table 6.

Example 70

A solution of the compound obtained in Example 68 (200 mg) and triethylamine (145 μl) in tetrahydrofuran (15 ml) is cooled to –20°C, and thereto is added a solution of acetyl chloride (61 mg) in tetrahydrofuran (5 ml). The reaction mixture is stirred at the same temperature for one hour, and warmed to room temperature. To the reaction mixture are added acetyl chloride (122 mg) and triethylamine (290 μl), and the mixture is stirred at room temperature overnight. To the reaction mixture are added ethyl acetate and water, and the ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; hexane:ethyl acetate = 2:1) to give 2-diacetylamino-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (75 mg) as listed in Table 6.

Example 71

The compound obtained in Example 67 (1.00 g) is dissolved in dimethylformamide (10 ml), and thereto are added potassium carbonate (382 mg) and methyl iodide (392 mg). The mixture is stirred at room temperature overnight, and thereto are added chloroform and water. The chloroform layer is separated, washed, dried, and concentrated under reduced pressure. The residue is crystallized from diethyl ether to give 3-methoxycarbonyl-2-(N-methyl-N-tert-

butoxycarbonylamino)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 6, which is used as a starting compound in Example 72 without further purification.

Example 72

The compound obtained in Example 71 is treated in the same manner as in Example 24 to give 3-methoxycarbonyl-2-(methylamino)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 6.

Example 73

The compound obtained in Example 67 and the corresponding starting compounds are treated in the same manner as in Example 10-(2) to give 2-[N-tert-butoxycarbonyl-N-(2-hydroxyethyl)amino]-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 6, which is used as a starting compound in Example 74 without further purification.

Example 74

To a solution of the compound obtained in Example 73 (170 mg) in dioxane (1 ml) is added a 4M solution of hydrogen chloride in dioxane (10 ml), and the mixture is stirred at room temperature for three hours. The reaction mixture is concentrated under reduced pressure, and the residue is dissolved in ethyl acetate. The mixture is washed with water, dried, and concentrated under reduced pressure. The residue is purified by Chromatotron (solvent; chloroform:acetone = 5:1), and crystallized from diethyl ether to give 2-[N-(2-hydroxyethyl)amino]-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 6.

Example 75

To a solution of the compound obtained in Example 74 (210 mg) in ethyl

acetate (10 ml) is added a 4M solution of hydrogen chloride in ethyl acetate (10 ml), and the mixture is stirred at room temperature for five hours. The reaction mixture is concentrated under reduced pressure, and the residue is dissolved in ethyl acetate. The solution is washed successively with a saturated aqueous sodium hydrogen carbonate solution and water, and dried. The solution is concentrated under reduced pressure, and the residue is purified by silica gel column chromatography (solvent; hexane:ethyl acetate = 2:1), and crystallized from diethyl ether to give 2-(2-acetoxyethylamino)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 6.

Example 76

(1) The compound obtained in Reference Example 51 and the corresponding starting compounds are treated in the same manner as in Example 10-(2) to give 2-(N-tert-butoxycarbonyl-N-n-propylamino)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone, which is used in the subsequent reaction without further purification.

(2) The compound thus obtained is treated in the same manner as in Example 24 to give 3-methoxycarbonyl-2-n-propylamino-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 6.

Example 77

The compound obtained in Reference Example 51 and the corresponding starting compounds are treated in the same manner as in Example 76 to give 2-ethylamino-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 6.

Example 78

The compound obtained in Reference Example 75 and the

corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give 2-[(1S)-1-benzyloxycarbonyl-2-phenylethyl]-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 6, which is used as a starting compound in Example 79 without further purification.

Example 79

The compound obtained in Example 78 is treated in the same manner as in Example 2 to give 2-[(1S)-1-carboxy-2-phenylethyl]-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 6.

Example 80

The compound obtained in Reference Example 75 and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give 2-(1H-1-methylbenztriazol-6-yl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 6.

Examples 81-85

6,7-Dimethoxy-4-(3,4,5-trimethoxyphenyl)-3-carboxylic acid (the compound obtained in Reference Example 50) and the corresponding starting compounds are treated in the same manner as in Example 1 or 31 to give the following compounds as listed in Table 7.

6,7-dimethoxy-2-(4-fluorophenyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 81);

6,7-dimethoxy-2-(3-methoxy-4-aminophenyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 82);

6,7-dimethoxy-2-[4-(2-hydroxyethyl)phenyl]-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 83);

6,7-dimethoxy-2-(3-hydroxyphenyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 84);

2-(N-tert-butoxycarbonyl-N-methylamino)-6,7-dimethoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 85), which is used as a starting compound in Example 86 without further purification.

Example 86

The compound obtained in Example 85 is treated in the same manner as in Example 24 to give 6,7-dimethoxy-3-methoxycarbonyl-2-methylamino-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 7.

Example 87

The compound obtained in Reference Example 50 and the corresponding starting compounds are treated in the same manner as in Example 1 or 39 to give 6,7-dimethoxy-3-methoxycarbonyl-2-[cis-(4-methoxycarbonyl)-cyclohexyl]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 7.

Example 88

The compound obtained in Example 87 is treated in the same manner as in Example 21 to give 2-(4-carboxycyclohexyl)-6,7-dimethoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 7.

Examples 89-91

The compound obtained in Reference Example 50 and the corresponding starting compounds are treated in the same manner as in Example 1 or 39 to give the following compounds as listed in Table 7.

6,7-dimethoxy-2-(2-furylmethyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 89);

6,7-dimethoxy-2-(2,3-dimethylphenyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 90);

6,7-dimethoxy-3-methoxycarbonyl-2-(3,4,5-trimethoxyphenyl)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 91);

Example 92

(1) The compound obtained in Reference Example 50 and the corresponding starting compounds are treated in the same manner as in Example 43 to give 2-(4-aminophenyl)-6,7-dimethoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 7.

(2) The compound thus obtained is treated in the same manner as in Example 9-(3) to give 2-(4-aminophenyl)-6,7-dimethoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 7.

Example 93

To a solution of the compound obtained in Example 92-(1) (156 mg) in methylene chloride (2 ml) are added dropwise triethylamine (0.138 ml) and methylsulfonyl chloride (78 µl), which are divided into three portions, under ice-cooling. The mixture is stirred for 15 minutes, and warmed to room temperature. To the mixture are added water and chloroform. The chloroform layer is washed, dried, and concentrated under reduced pressure. The residue is crystallized from ethyl acetate to give 6,7-dimethoxy-2-{4-[N,N-bis(methylsulfonyl)amino]phenyl}-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 7.

Example 94

To a solution of formic acid (34 µl) in methylene chloride (2 ml) is added acetic anhydride (85 µl) under ice-cooling, and the mixture is stirred for 30

minutes. To the reaction mixture is added dropwise a solution of the compound obtained in Example 92-(1) (312 mg) in methylene chloride (1 ml), and the mixture is stirred for two hours. The reaction is warmed to room temperature, and thereto are added water and methylene chloride. The methylene chloride layer is washed, dried, and concentrated under reduced pressure. The residue is crystallized from diethyl ether to give 2-(4-acetylaminophenyl)-6,7-dimethoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (270 mg) as listed in Table 7.

Example 95

To a solution of the compound obtained in Example 94 (260 mg) in tetrahydrofuran (3 ml) is added 60 % sodium hydride (28 mg) under ice-cooling, and the mixture is stirred at room temperature for 30 minutes. To the reaction mixture is added dropwise methyl iodide (58 μl), and the mixture is stirred for five hours. To the reaction mixture are added dilute hydrochloric acid and chloroform. The chloroform layer is separated, washed, dried, and concentrated under reduced pressure. To the residue is added a mixture of methanol and 2M hydrochloric acid (1:1) (10 ml), and the mixture is heated under reflux for 16 hours. The reaction mixture is cooled to room temperature, and concentrated under reduced pressure to remove the methanol. To the resulting aqueous layer is added aqueous sodium hydrogen carbonate solution to adjust the pH value to pH 8. The mixture is extracted with chloroform. The extract is washed with water, dried, and concentrated under reduced pressure. The residue is crystallized from diethyl ether to give 6,7-dimethoxy-3-methoxycarbonyl-2-[4-(methylamino)phenyl]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (170 mg) as listed in Table 7.

Examples 96-98

The compound obtained in Reference Example 50 and the corresponding starting compounds are treated in the same manner as in Example 1 or 39 to give the following compounds as listed in Table 7.

6,7-dimethoxy-3-methoxycarbonyl-2-piperidino-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 96);

6,7-dimethoxy-3-methoxycarbonyl-2-(3,4-methylenedioxybenzyl)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 97);

6,7-dimethoxy-3-methoxycarbonyl-2-(3,4-methylenedioxyphenyl)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 98);

Example 99

(1) A mixture of a solution of 6,7-dimethoxy-4-(3,4,5-trimethoxyphenyl)-isocoumarin-3-carboxylic acid (the compound obtained in Reference Example 50) (2.4 g) in methanol (50 ml) and a 5.5M solution of ammonia in methanol (50 ml) is stirred at room temperature overnight. The reaction solution is concentrated under reduced pressure to remove the ammonia, and further the solvent is distilled off. The residue thus obtained is extracted with chloroform, and the extract is washed with water, dried, and concentrated under reduced pressure. To the residue is added a 4M solution of hydrogen chloride in ethyl acetate (30 ml), and the mixture is stirred at room temperature overnight. The mixture is concentrated under reduced pressure, and the resulting residue is extracted with chloroform. The extract is washed with water, dried, and concentrated under reduced pressure to give 3-carboxy-6,7-dimethoxy-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (1.89 g) as listed in Table 8.

(2) The compound thus obtained (1.50 g) is dissolved with heating in 2M

aqueous sodium hydroxide solution (1.8 ml) and water (20 ml). The mixture is allowed to stand at room temperature, and the precipitated crystals are collected by filtration to give 3-carboxy-6,7-dimethoxy-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone sodium salt as listed in Table 8.

Example 100

The compound obtained in Reference Example 50 and the corresponding starting compounds are treated in the same manner as in Example 99-(1) to give 3-carboxy-6,7-dimethoxy-2-(2-piperidinoethyl)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 8.

Examples 101-106

The compound obtained in Reference Example 50 and the corresponding starting compounds are treated in the same manner as in Example 1 or 39 to give the following compounds as listed in Table 9.

6,7-dimethoxy-3-methoxycarbonyl-2-(4-methyl-1-piperazinyl)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 101);

6,7-dimethoxy-3-methoxycarbonyl-2-phenyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 102);

2-(4-chlorophenyl)-6,7-dimethoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 103);

2-(3-chlorophenyl)-6,7-dimethoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 104);

2-cyclopentyl-6,7-dimethoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 105);

2-benzyl-6,7-dimethoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 106);

Examples 107-108

The compound obtained in Reference Example 50 and the corresponding starting compounds are treated in the same manner as in Example 43 to give the following compounds as listed in Table 9.

6,7-dimethoxy-2-(4-dimethylaminophenyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 107);

6,7-dimethoxy-3-methoxycarbonyl-2-(4-morpholinophenyl)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 108);

Examples 109-111

The compound obtained in Reference Example 50 and the corresponding starting compounds are treated in the same manner as in Example 1 or 39 to give the following compounds as listed in Table 9.

6,7-dimethoxy-2-[3-(1-imidazolyl)propyl]-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 109);

6,7-dimethoxy-2-[3-(hydroxymethyl)phenyl]-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 110);

6,7-dimethoxy-3-methoxycarbonyl-2-[4-(methoxycarbonylmethyl)-phenyl]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 111);

Example 112

(1) The compound obtained in Example 111 is treated in the same manner as in Example 21 to give 2-[4-(carboxymethyl)phenyl]-6,7-dimethoxy-3-methoxy-carbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone.

(2) The compound thus obtained is treated in the same manner as in Example 99-(2) to give 2-[4-(carboxymethyl)phenyl]-6,7-dimethoxy-3-methoxy-carbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone sodium salt as listed

in Table 9.

Example 113

The compound obtained in Example 99-(1) (2 g) is suspended in methanol (20 ml), and thereto is added conc. sulfuric acid (5 ml) at room temperature. The mixture is heated under reflux for 8 hours, and poured into an aqueous potassium carbonate solution under ice-cooling. The mixture is extracted with chloroform, and the extract is washed, dried, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; chloroform) to give 6,7-dimethoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (1.75 g) as listed in Table 9.

Example 114

To a solution of the compound obtained in Example 113 (1.4 g) in dimethylformamide (15 ml) are added 4-picolyl chloride hydrochloride (588 mg) and potassium carbonate (1.13 g), and the mixture is stirred at 50°C for two hours. After the reaction is complete, to the mixture are added ethyl acetate and water. The mixture is extracted with ethyl acetate, and the extract is washed, dried, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; chloroform:acetone = 10:1). The residue is dissolved in ethyl acetate, and thereto is added a 4M solution of hydrogen chloride in ethyl acetate (1 ml). The precipitated crystals are collected by filtration, washed with ethyl acetate to give 6,7-dimethoxy-3-methoxycarbonyl-2-(4-pyridylmethyl)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (820 mg) as listed in Table 9.

Example 115

To a solution of the compound obtained in Example 113 (1.4 g) in

dimethylformamide (15 ml) are added cyclopropylmethyl bromide (484 mg) and potassium carbonate (1.13 g), and the mixture is stirred at 50°C for one hour. To the mixture are added ethyl acetate and water, and the ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; chloroform:hexane: ethyl acetate = 5:5:1) to give 2-cyclopropylmethyl-6,7-dimethoxy-3-methoxy-carbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (840 mg) as listed in Table 9.

Examples 116-117

The compound obtained in Example 113 and the corresponding starting compounds are treated in the same manner as in Example 114 to give the following compounds as listed in Table 9.

6,7-dimethoxy-3-methoxycarbonyl-2-(3-pyridylmethyl)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 116);

6,7-dimethoxy-3-methoxycarbonyl-2-(2-pyridylmethyl)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 117);

Example 118

The compound obtained in Reference Example 50 and the corresponding starting compounds are treated in the same manner as in Example 1 or 39 to give 6,7-dimethoxy-3-methoxycarbonyl-2-morpholino-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 9.

Example 119

A mixture of the compound obtained in Example 118 (1.3 g), conc. hydrochloric acid (15 ml) and dioxane (15 ml) is heated under reflux overnight. The reaction mixture is cooled to room temperature, and thereto are added water

and chloroform. The extract is washed, dried, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; chloroform:acetone = 50:1) to give 6,7-dimethoxy-4-(3,5-dimethoxy-4-hydroxyphenyl)-3-methoxycarbonyl-2-morpholino-1(2H)-isoquinolinone (530 mg) as listed in Table 10.

Example 120

6,7-Dimethoxy-3-hydroxy-4-(3,4,5-trimethoxyphenyl)-3,4-dihydroisocoumarin-3-carboxylic acid (the compound obtained in Reference Example 74) and the corresponding starting compounds are treated in the same manner as in Example 46 to give 6,7-dimethoxy-3-methoxycarbonyl-2-[(2-pyridyl)amino]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 11.

Example 121

The compound obtained in Reference Example 50 and the corresponding starting compounds are treated in the same manner as in Example 1 or 39 to give 6,7-dimethoxy-3-methoxycarbonyl-2-(3-methylthiophenyl)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 11.

Example 122

To a solution of the compound obtained in Example 121 (200 mg) in chloroform (15 ml) is added dropwise a solution of m-chloroperbenzoic acid (164 mg) in chloroform (10 ml) at room temperature, and the mixture is stirred overnight. The reaction mixture is washed with a 5 % aqueous sodium hydroxide solution, and concentrated under reduced pressure to give 6,7-dimethoxy-3-methoxycarbonyl-2-(3-methylsulfonylphenyl)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (150 mg) as listed in Table 11.

Example 123

To a solution of the compound obtained in Example 121 (200 mg) in chloroform (15 ml) is added a solution of m-chloroperbenzoic acid (78 mg) in chloroform (10 ml) at room temperature, and the mixture is stirred for one hour. The reaction mixture is washed with a 5 % aqueous sodium hydroxide solution, dried, and concentrated under reduced pressure to give 6,7-dimethoxy-3-methoxycarbonyl-2-(3-methylsulfinylphenyl)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (1750 mg) as listed in Table 11.

Example 124

The compound obtained in Reference Example 50 and the corresponding starting compounds are treated in the same manner as in Example 1 or 39 to give 6,7-dimethoxy-2-(tetrahydro-4H-1,4-thiazin-4-yl)-3-methoxy-carbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 11.

Example 125

The compound obtained in Example 124 is treated in the same manner as in Example 122 to give 6,7-dimethoxy-2-(1,1-dioxo-tetrahydro-4H-1,4-thiazin-4-yl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 11.

Example 126

The compound obtained in Example 124 is treated in the same manner as in Example 123 to give 6,7-dimethoxy-2-(1-oxo-tetrahydro-4H-1,4-thiazin-4-yl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 11.

Example 127

(1) To a solution of 2-(3,4,5-trimethoxybenzoyl)-4,5-dimethoxybenzoic acid

(the compound obtained in Reference Example 14) (10.0 g), sarcosine methyl ester (5.38 g) and 1-hydroxybenzotriazole (4.48 g) in dimethylformamide (100 ml) are added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5.60 g) and triethylamine (4.89 ml) under ice-cooling, and the mixture is stirred at room temperature overnight. To the reaction mixture are added water and ethyl acetate. The ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure. The resulting residue is crystallized from diethyl ether to give N-methoxycarbonylmethyl-N-methyl-2-(3,4,5-trimethoxybenzoyl)-4,5-dimethoxybenzene carboxamide (10.1 g).

(2) To a solution of the compound (5.70 g) in tetrahydrofuran (130 ml) is added potassium tert-butoxide (2.08 g) under ice-cooling, and the mixture is stirred at room temperature for 30 minutes. To the reaction mixture are added water and ethyl acetate, and the ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure. The precipitated crystals are dissolved in chloroform (100 ml), and thereto is added p-toluenesulfonic acid (4.70 g). The mixture is refluxed for two hours, and the reaction mixture is washed, dried, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; hexane:ethyl acetate = 1:2) to give 6,7-dimethoxy-3-methoxycarbonyl-2-methyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (2.46 g) as listed in Table 12.

Example 128

The compound obtained in Example 127 is treated in the same manner as in Example 21 to give 3-carboxy-6,7-dimethoxy-2-methyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 12.

Example 129

A solution of the compound obtained in Example 128 (1.50 g), 1,3-dicyclohexylcarbodiimide (793 mg) and 1-hydroxybenzotriazole (588 mg) in dimethylformamide (30 ml) is stirred at room temperature for one hour, and thereto is added morpholine (335 mg), and the mixture is stirred for two hours. The mixture is further stirred at 50°C for four hours. To the reaction mixture are added water and ethyl acetate. The ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure. The residue is crystallized from diethyl ether-ethyl acetate to give 6,7-dimethoxy-2-methyl-3-morphlino-carbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (893 mg) as listed in Table 12.

Example 130

To a mixture of methylene chloride (10 ml) and dimethylformamide (5 ml) are added the compound obtained in Example 128 (1.66 g), 1,3-dicyclohexyl-carbodiimide (960 mg) and 1-hydroxybenzotriazole (710 mg), and the mixture is stirred at room temperature for 30 minutes. To the reaction mixture is added a solution of 4-(2-aminoethyl)imidazole (850 mg) and triethylamine (1.28 ml) in dimethylformamide (5 ml), and the mixture is stirred for three hours, and then further stirred at 50°C for 7 hours. To the reaction mixture are added water and ethyl acetate. The ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; chloroform:hexane = 30:1) to give 6,7-dimethoxy-3-[2-(4-imidazolyl)ethylaminocarbonyl]-2-methyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (1.0 g) as listed in Table 12.

Example 131

The compound obtained in Example 128 and the corresponding starting

compounds are treated in the same manner as in Example 130 to give 6,7-dimethoxy-3-[4-(2-hydroxyethyl)piperazinocarbonyl]-2-methyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 12.

Example 132

The compound obtained in Reference Example 50 and the corresponding starting compounds are treated in the same manner as in Example 39 to give 6,7-dimethoxy-2-(3-methoxy-4-aminophenyl)-4-(3,4,5-trimethoxyphenyl)-3-trimethylsilylmethyloxycarbonyl-1(2H)-isoquinolinone as listed in Table 12.

Example 133

6,7-Diethoxy-4-(3,4,5-trimethoxyphenyl)isocoumarin-3-carboxylic acid (the compound obtained in Reference Example 54) and the corresponding starting compounds are treated in the same manner as in Example 1 or 39 to give 6,7-diethoxy-3-methoxycarbonyl-2-morpholino-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 13.

Examples 134-135

6,7-Diethoxy-3-hydroxy-4-(3,4,5-trimethoxyphenyl)-3,4-dihydroisocoumarin-3-carboxylic acid (the compound obtained in Reference Example 76) and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give the following compounds as listed in Table 13.

6,7-diethoxy-3-methoxycarbonyl-2-(4-tetrahydropyranyl)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 134);

2-[4-(tert-butoxycarbonylamino)phenyl]-6,7-diethoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 135);

Example 136

(1) The compound obtained in Example 135 is treated in the same manner as in Example 24 to give 2-(4-aminophenyl)-6,7-diethoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 13.

(2) The compound thus obtained is treated in the same manner as in Example 33-(2) to give 2-(4-aminophenyl)-6,7-diethoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 13.

Example 137

The compound obtained in Example 135 is treated in the same manner as in Example 71 to give 6,7-diethoxy-3-methoxycarbonyl-2-[4-(N-methyl-N-tert-butoxycarbonylamino)phenyl]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 13.

Example 138

The compound obtained in Example 137 is treated in the same manner as in Example 24 to give 6,7-diethoxy-3-methoxycarbonyl-2-[4-(methylamino)-phenyl]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 13.

Example 139

The compound obtained in Reference Example 76 and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give 2-(4-benzyloxyphenyl)-6,7-diethoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 13.

Example 140

The compound obtained in Example 139 is treated in the same manner as in Example 2 to give 6,7-diethoxy-2-(4-hydroxyphenyl)-3-methoxycarbonyl-4-

(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 13.

Examples 141-147

5-Substituted, 6-substituted, 7-substituted or 6,7-disubstituted-4-(3,4,5-trimethoxyphenyl)isocoumarin-3-carboxylic acid compounds (the compounds obtained in Reference Example 58, 57, 53, 52, 56, 59 or 55) and the corresponding starting compounds are treated in the same manner as in Example 1 or 39 to give the following compounds as listed in Table 14.

3-methoxycarbonyl-6-methyl-2-phenyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 141);

6-chloro-3-methoxycarbonyl-2-phenyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 142);

3-methoxycarbonyl-6,7-methylenedioxy-2-phenyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 143);

7-methoxy-3-methoxycarbonyl-2-phenyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 144);

8-chloro-3-methoxycarbonyl-2-phenyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 145);

8-methoxy-3-methoxycarbonyl-2-phenyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 146);

6-methoxy-3-methoxycarbonyl-2-phenyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 147);

Example 148

8-Chloro-3-hydroxy-4-(3,4,5-trimethoxyphenyl)-3,4-dihydro-isocoumarin-3-carboxylic acid (the compound obtained in Reference Example 78) and the corresponding starting compounds are treated in the same manner

as in Example 4 or 31 to give 2-[4-(tert-butoxycarbonylamino)phenyl]-8-chloro-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 14.

Example 149

The compound obtained in Example 148 is treated in the same manner as in Example 24 to give 2-(4-aminophenyl)-8-chloro-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 14.

Example 150

3-Hydroxy-4-(3,4,5-trimethoxyphenyl)-6-methoxy-3,4-dihydro-isocoumarin-3-carboxylic acid (the compound obtained in Reference Example 77) and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give 2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 14.

Example 151

The compound obtained in Example 150 is treated in the same manner as in Example 8-(1) to give 2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 14.

Example 152

4-(3-Bromo-4,5-dimethoxyphenyl)-6,7-dimethoxyisocoumarin-3-carboxylic acid (the compound obtained in Reference Example 60) and the corresponding starting compounds are treated in the same manner as in Example 10-(1) to give 4-(3-bromo-4,5-dimethoxyphenyl)-3-carboxy-6,7-dimethoxy-2-phenyl-1(2H)-isoquinolinone as listed in Table 15.

Example 153

The corresponding starting compounds are treated in the same manner as in Example 10-(2) to give 4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-2-phenyl-1(2H)-isoquinolinone as listed in Table 15.

Examples 154-155

The compound obtained in Example 152 and the corresponding starting compounds are treated in the same manner as in Example 129 to give the following compounds as listed in Table 15.

4-(3-bromo-4,5-dimethoxyphenyl)-3-carbamoyl-6,7-dimethoxy-2-phenyl-1(2H)-isoquinolinone (Example 154);

4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-(N-methyl-carbamoyl)-2-phenyl-1(2H)-isoquinolinone (Example 155);

Examples 156-160

4-(3-Bromo-4,5-dimethoxyphenyl)-3-hydroxy-6,7-dimethoxy-isocoumarin-3-carboxylic acid (the compound obtained in Reference Example 80) and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give the following compounds as listed in Table 16.

4-(3-bromo-4,5-dimethoxyphenyl)-2-(4-bromo-3-methylphenyl)-6,7-dimethoxy-3-methoxycarbonyl-1(2H)-isoquinolinone (Example 156);

4-(3-bromo-4,5-dimethoxyphenyl)-2-(4-carbamoylphenyl)-6,7-dimethoxy-3-methoxycarbonyl-1(2H)-isoquinolinone (Example 157);

4-(3-bromo-4,5-dimethoxyphenyl)-2-(3-carbamoylphenyl)-6,7-dimethoxy-3-methoxycarbonyl-1(2H)-isoquinolinone (Example 158);

4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-2-methoxycarbonylmethyl-1(2H)-isoquinolinone (Example 159);

4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-2-ethoxycarbonyl-

methyl-3-methoxycarbonyl-1(2H)-isoquinolinone (Example 160);

Example 161

The compound obtained in Example 159 is treated in the same manner as in Example 21 to give 4-(3-bromo-4,5-dimethoxyphenyl)-2-carboxymethyl-6,7-dimethoxy-3-methoxycarbonyl-1(2H)-isoquinolinone as listed in Table 16.

Examples 162-164

The compound obtained in Reference Example 80 and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give the following compounds as listed in Table 16.

4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-2-[2-(2-hydroxyethyl-oxy)ethyl]-3-methoxycarbonyl-1(2H)-isoquinolinone (Example 162);

4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-2-(1-pyrrolyl)-1(2H)-isoquinolinone (Example 163);

4-(3-bromo-4,5-dimethoxyphenyl)-2-[2-(tert-butoxycarbonylamino)-ethyl]-6,7-dimethoxy-3-methoxycarbonyl-1(2H)-isoquinolinone (Example 164);

Example 165

The compound obtained in Example 164 is treated in the same manner as in Example 24 to give 2-(2-aminoethyl)-4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-1(2H)-isoquinolinone hydrochloride as listed in Table 16.

Example 166

The compound obtained in Reference Example 80 and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give 4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-2-(5-methylisoxazol-3-yl)-1(2H)-isoquinolinone as listed in

Table 16.

Example 167

4-(3-Bromo-4,5-dimethoxyphenyl)-6,7-dimethoxyisocoumarin-3-carboxylic acid (the compound obtained in Reference Example 60) and the corresponding starting compounds are treated in the same manner as in Example 1 or 39 to give 4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxy-carbonyl-2-(N-phenylamino)-1(2H)-isoquinolinone as listed in Table 16.

Examples 168-169

The compound obtained in Reference Example 80 and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give the following compounds as listed in Table 16.

4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-2-(3-nitrophenyl)-1(2H)-isoquinolinone (Example 168);

4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-2-(2-methoxyethyl)-1(2H)-isoquinolinone (Example 169);

Example 170

(1) The compound obtained in Reference Example 80 and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give 4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxy-carbonyl-2-(3-methoxycarbonylphenyl)-1(2H)-isoquinolinone.

(2) The compound thus obtained is treated in the same manner as in Example 21 to give 4-(3-bromo-4,5-dimethoxyphenyl)-2-(3-carboxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-1(2H)-isoquinolinone as listed in Table 16.

Example 171

The compound obtained in Example 170 is treated in the same manner as

in Example 129 to give 4-(3-bromo-4,5-dimethoxyphenyl)-2-{3-[2-(tert-butoxy-carbonyl)hydrazinocarbonyl]phenyl}-6,7-dimethoxy-3-methoxycarbonyl-1(2H)-isoquinolinone as listed in Table 16.

Example 172

The compound obtained in Example 171 is treated in the same manner as in Example 68 to give 4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-2-[3-(hydrazinocarbonyl)phenyl]-3-methoxycarbonyl-1(2H)-isoquinolinone as listed in Table 16.

Example 173

The compound obtained in Reference Example 80 and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give 4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxy-carbonyl-2-[3-(methoxycarbonylmethoxy)phenyl]-1(2H)-isoquinolinone as listed in Table 16.

Example 174

The compound obtained in Example 173 is treated in the same manner as in Example 21 to give 4-(3-bromo-4,5-dimethoxyphenyl)-2-[3-(carboxy-methoxy)phenyl]-6,7-dimethoxy-3-methoxycarbonyl-1(2H)-isoquinolinone as listed in Table 16.

Example 175

The compound obtained in Example 174 is treated in the same manner as in Example 129 to give 4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-2-{3-[N-(3-morpholinopropyl)carbamoylmethyloxy]phenyl}-1(2H)-isoquinolinone as listed in Table 16.

Example 176

The compound obtained in Reference Example 80 and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give 2-(3-aminophenyl)-4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-1(2H)-isoquinolinone as listed in Table 16.

Example 177

To formic acid (3 ml) is added acetic anhydride (3 ml), and the mixture is stirred at room temperature for four hours. To the reaction mixture is added the compound obtained in Example 176 (500 mg), and the mixture is stirred at room temperature overnight. The mixture is further stirred at 60°C overnight. After the reaction is complete, to the reaction mixture are added water and ethyl acetate. The ethyl acetate layer is separated, washed with water, dried, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; chloroform:acetone= 10:1) to give 6,7-dimethoxy-2-[3-(formylamino)phenyl]-4-(3-bromo-4,5-dimethoxyphenyl)-3-methoxycarbonyl-1(2H)-isoquinolinone as listed in Table 16.

Examples 178-180

The compound obtained in Reference Example 80 and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give the following compounds as listed in Table 16.

4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-2-[3-(2-methylpyrimidin-4-yl)phenyl]-1(2H)-isoquinolinone (Example 178);

4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-2-[3-(1-methylpyrazol-3-yl)phenyl]-1(2H)-isoquinolinone (Example 179);

4-(3-bromo-4,5-dimethoxyphenyl)-2-{2-[4-(tert-butoxycarbonyl)-piperazin-1-yl]ethyl}-6,7-dimethoxy-3-methoxycarbonyl-1(2H)-isoquinolinone

(Example 180);

Example 181

The compound obtained in Example 180 is treated in the same manner as in Example 24 to give 4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-2-(2-piperazinoethyl)-3-methoxycarbonyl-1(2H)-isoquinolinone dihydrochloride as listed in Table 16.

Example 182

The compound obtained in Reference Example 60 and the corresponding starting compounds are treated in the same manner as in Example 39, and further treated in the same manner as in Example 43-(2) to give 4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-2-(2-morpholinoethyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 16.

Example 183

The compound obtained in Reference Example 60 and the corresponding starting compounds are treated in the same manner as in Example 1 or 39 to give 2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-1(2H)-isoquinolinone as listed in Table 16.

Example 184

The compound obtained in Reference Example 80 and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give 4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-2-(3-hydroxypropyl)-3-methoxycarbonyl-1(2H)-isoquinolinone as listed in Table 16.

Example 185

To a solution of the compound obtained in Example 184 (190 mg) in dimethylformamide (3 ml) are added nicotinoyl chloride (69 mg) and

triethylamine (0.11 ml), and the mixture is stirred at room temperature overnight. To the reaction mixture are added nicotinoyl chloride (69 mg) and triethylamine (0.11 ml), and the mixture is stirred overnight. After the reaction is complete, to the mixture are added ethyl acetate and water. The ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure to give 4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-2-[3-(nicotinoyloxy)propyl]-1(2H)-isoquinolinone (170 mg) as listed in Table 16.

Examples 186-198

The compound obtained in Reference Example 80 and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give the following compounds as listed in Table 16.

2-n-butyl-4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-1(2H)-isoquinolinone (Example 186);

4-(3-bromo-4,5-dimethoxyphenyl)-2-carbamoylmethyl-6,7-dimethoxy-3-methoxycarbonyl-1(2H)-isoquinolinone (Example 187);

4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-2-(6-quinolyl)-1(2H)-isoquinolinone (Example 188);

4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-2-(2-tetrahydrofurylmethyl)-1(2H)-isoquinolinone (Example 189);

4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-2-(3-quinolyl)-1(2H)-isoquinolinone (Example 190);

4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-2-[(1-hydroxymethyl-2-hydroxy)ethyl]-3-methoxycarbonyl-1(2H)-isoquinolinone (Example 191);

4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-2-(3-dimethylamino-propyl)-3-methoxycarbonyl-1(2H)-isoquinolinone (Example 192);

4-(3-bromo-4,5-dimethoxyphenyl)-2-[3-(tert-butoxycarbonylamino)-propyl]-6,7-dimethoxy-3-methoxycarbonyl-1(2H)-isoquinolinone (Example 193);

4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-2-(3-methoxypropyl)-1(2H)-isoquinolinone (Example 194);

2-(N-benzylpiperidin-4-yl)-4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-1(2H)-isoquinolinone (Example 195);

2-benzyl-4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxy-carbonyl-1(2H)-isoquinolinone (Example 196);

4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-2-propyl-1(2H)-isoquinolinone (Example 197);

2-[3-(6-amino)pyridyl]-4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-1(2H)-isoquinolinone (Example 198);

Examples 199-201

The compound obtained in Reference Example 80 and the corresponding starting compounds are treated in the same manner as in Example 46 to give the following compounds as listed in Table 16.

2-(4-aminopropyl)-4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-1(2H)-isoquinolinone hydrochloride (Example 199);

2-(cis-2-amino-1-hexyl)-4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-1(2H)-isoquinolinone (Example 200);

2-(4-aminocyclohexyl)-4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-1(2H)-isoquinolinone hydrochloride (Example 201);

Example 202

The compound obtained in Reference Example 60 and the corresponding starting compounds are treated in the same manner as in Example 1 or 39 to give 2-(4-acetylaminophenyl)-4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-1(2H)-isoquinolinone as listed in Table 16.

Examples 203-204

The compound obtained in Reference Example 60 and the corresponding starting compounds are treated in the same manner as in Example 1 or 39 to give the following compounds as listed in Table 16.

4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-2-morpholino-1(2H)-isoquinolinone (Example 203);

2-[(4-benzyloxycarbonyl)piperazin-1-yl]-4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-1(2H)-isoquinolinone (Example 204);

Examples 205-206

The compound obtained in Example 204 (550 mg) is dissolved in a 25 % solution of hydrogen bromide in acetic acid (2.5 ml), and the mixture is stirred at room temperature for 15 minutes. To the reaction mixture are added ethyl acetate and a saturated aqueous sodium hydrogen carbonate solution. The ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure. The resulting residue is dissolved in acetonitrile (3 ml), and thereto are added 2-bromoethanol (99 mg) and potassium carbonate (65 mg). The reaction mixture is heated under reflux for three hours. The reaction solution is warmed to room temperature, and thereto are added ethyl acetate and a saturated aqueous sodium hydrogen carbonate solution. The ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure. The residue

is purified by silica gel column chromatography (solvent; chloroform:methanol = 20:1) to give 4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-2-[4-(2-hydroxyethyl)piperazin-1-yl]-3-methoxycarbonyl-1(2H)-isoquinolinone as listed in Table 16. The compound thus obtained is dissolved in chloroform (3 ml), and thereto is added a 4M solution of hydrogen chloride in ethyl acetate (50 µl). The reaction mixture is concentrated under reduced pressure, and to the residue is added diethyl ether. The resulting crystals are collected by filtration to give 4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-2-[4-(2-hydroxyethyl)-piperazin-1-yl]-3-methoxycarbonyl-1(2H)-isoquinolinone hydrochloride (Example 205) as listed in Table 16. During the above reaction (the reaction of the compound obtained in Example 204 with 2-bromoethanol), 2-(4-benzyl-piperazin-1-yl)-4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxy-carbonyl-1(2H)-isoquinolinone (Example 206) as listed in Table 16 is obtained as a by-product.

Example 207

The compound obtained in Example 193 is treated in the same manner as in Example 24 to give 2-(4-aminopropyl)-4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-1(2H)-isoquinolinone hydrochloride as listed in Table 16.

Example 208

4-(4-Bromo-3,5-dimethoxyphenyl)-3-hydroxy-6,7-dimethoxy-3,4-dihydroisocoumarin-3-carboxylic acid (the compound obtained in Reference Example 81) and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to 2-[4-(tert-butoxycarbonylamino)phenyl]-4-(4-bromo-3,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-1(2H)-

isoquinolinone, which is further treated in the same manner as in Example 24 to give 2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-1(2H)-isoquinolinone hydrochloride as listed in Table 17.

Example 209

4-(3,5-Dimethoxyphenyl)-3-hydroxy-6,7-dimethoxy-3,4-dihydro-isocoumarin-3-carboxylic acid (the compound obtained in Reference Example 83) and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to 2-[4-(tert-butoxycarbonylamino)phenyl]-6,7-dimethoxy-4-(3,5-dimethoxyphenyl)-3-methoxycarbonyl-1(2H)-isoquinolinone, which is further treated in the same manner as in Example 24 to give 2-(4-amino-phenyl)-6,7-dimethoxy-4-(3,5-dimethoxyphenyl)-3-methoxycarbonyl-1(2H)-isoquinolinone hydrochloride as listed in Table 17.

Examples 210-211

The corresponding 6,7-dimethoxyisocoumarin-3-carboxylic acid compounds (the compounds obtained in Reference Example 61 or 63) and the corresponding starting compounds are treated in the same manner as in Example 1 or 39 to give the following compounds as listed in Table 17.

4-(4-bromo-3,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-2-morpholino-1(2H)-isoquinolinone (Example 210);

6,7-dimethoxy-4-(3,5-dimethoxyphenyl)-3-methoxycarbonyl-2-morpholino-1(2H)-isoquinolinone (Example 211);

Example 212

6,7-Dimethoxy-4-(2,3,4-trimethoxyphenyl)isocoumarin-3-carboxylic acid (the compound obtained in Reference Example 64) and the corresponding starting compounds are treated in the same manner as in Example 1 or 39 to give

6,7-dimethoxy-3-methoxycarbonyl-2-phenyl-4-(2,3,4-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 17.

Example 213

7-Benzyloxy-3-hydroxy-6-methoxy-4-(3,4,5-trimethoxyphenyl)-3,4-dihydroisocoumarin-3-carboxylic acid (the compound obtained in Reference Example 71) and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give 7-benzyloxy-6-methoxy-3-methoxycarbonyl-2-phenyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 18.

Example 214

The compound obtained in Example 213 treated in the same manner as in Example 2 to give 7-hydroxy-6-methoxy-3-methoxycarbonyl-2-phenyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 18.

Examples 215-217

The compound obtained in Example 214 is treated in the same manner as in Example 3 to give the following compounds as listed in Table 18.

6-methoxy-3-methoxycarbonyl-2-phenyl-4-(3,4,5-trimethoxyphenyl)-7-(4-pyridylmethyloxy)-1(2H)-isoquinolinone hydrochloride (Example 215);

6-methoxy-3-methoxycarbonyl-2-phenyl-4-(3,4,5-trimethoxyphenyl)-7-(3-pyridylmethyloxy)-1(2H)-isoquinolinone hydrochloride (Example 216);

6-methoxy-3-methoxycarbonyl-2-phenyl-4-(3,4,5-trimethoxyphenyl)-7-(2-pyridylmethyloxy)-1(2H)-isoquinolinone hydrochloride (Example 217);

Example 218

Pyrrol-2-carboxylic acid (38.4 mg) and 1-hydroxybenzotriazole monohydrate (53 mg) are dissolved in acetonitrile (10 ml), and thereto is added

1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (66.3 mg), and the mixture is stirred at room temperature for 30 minutes. The reaction mixture is added to a solution of the compound obtained in Example 214 (162 mg) and potassium carbonate (48 mg) in dimethylformamide (10 ml), and the mixture is stirred at room temperature for 30 minutes. Water and ethyl acetate are added to the reaction mixture. The ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure. The residue is crystallized from diethyl ether to give 6-methoxy-3-methoxycarbonyl-2-phenyl-7-(2-pyrrolylcarbonyl-oxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (145 mg) as listed in Table 18.

Examples 219-220

The compound obtained in Example 214 is treated in the same manner as in Example 7-(1) to give the compounds as listed in Table 18.

6-methoxy-3-methoxycarbonyl-2-phenyl-7-(2-thienylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 219);

6-methoxy-3-methoxycarbonyl-7-{[(1-methyl-2-methoxycarbonyl)-pyrrol-4-yl]methyloxy}-2-phenyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 220);

Example 221

7-Benzyloxy-3-hydroxy-4-(3,4,5-trimethoxyphenyl)-3,4-dihydro-isocoumarin-3-carboxylic acid (the compound obtained in Reference Example 73) and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give 2-[4-(tert-butoxycarbonylamino)phenyl]-7-benzyl-oxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 19.

Example 222

The compound obtained in Example 221 is treated in the same manner as in Example 24 to give 2-(4-aminophenyl)-7-benzyloxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 19.

Example 223

The compound obtained in Example 221 is treated in the same manner as in Example 5 to give 2-[4-(tert-butoxycarbonylamino)phenyl]-7-hydroxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 19.

Example 224

The compound obtained in Example 223 is treated in the same manner as in Example 24 to give 2-(4-aminophenyl)-7-hydroxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 19.

Example 225

The compound obtained in Example 223 is treated in the same manner as in Example 6 or 7 to give 2-(4-aminophenyl)-3-methoxycarbonyl-7-(2-quinolylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride as listed in Table 19.

Examples 226-227

The compound obtained in Example 223 is treated in the same manner as in Example 6 or 7 to give the following compounds as listed in Table 19.

2-(4-aminophenyl)-3-methoxycarbonyl-7-(4-quinolylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 226);

2-(4-aminophenyl)-3-methoxycarbonyl-7-(3-quinolylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 227);

Example 228

The compound obtained in Example 4 is treated in the same manner as in Example 6-(2) to give 2-(4-aminophenyl)-7-benzyloxy-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 20.

Example 229

The compound obtained in Example 5 is treated in the same manner as in Example 6-(2) to give 2-(4-aminophenyl)-7-hydroxy-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 20.

Examples 230-238

The compound obtained in Example 5 and the corresponding starting compounds are treated in the same manner as in Example 6 to give the following compounds as listed in Table 20.

2-[4-(tert-butoxycarbonylamino)phenyl]-7-(tert-butoxycarbonylmethyloxy)-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 230 (1));

2-(4-aminophenyl)-7-(carboxymethyloxy)-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 230 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-7-cyclopentyloxy-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 231 (1));

2-(4-aminophenyl)-7-cyclopentyloxy-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 231 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-7-[2-(N,N-dimethylamino)ethyloxy]-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 232 (1));

2-(4-aminophenyl)-7-[2-(N,N-dimethylamino)ethyloxy]-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 232 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-7-[2-(2-methoxyethyloxy)ethyloxy]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 233 (1));

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-[2-(2-methoxyethyloxy)ethyloxy]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 233 (2));

7-ethoxy-2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 234 (1));

2-(4-aminophenyl)-7-ethoxy-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 234 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-7-(2-methoxyethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 235 (1));

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(2-methoxyethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example

235 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-7-(4-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 236 (1));

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(4-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 236 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-7-(3-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 237 (1));

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(3-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 237 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-7-(2-quinolylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 238 (1));

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(2-quinolylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 238 (2));

Example 239

(1) The compound obtained in Example 5 and the corresponding starting compounds are treated in the same manner as in Example 6-(1) to give 2-[4-(tert-butoxycarbonylamino)phenyl]-7-(2-hydroxyethyloxy)-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 20.

(2) The compound thus obtained is treated in the same manner as in Example

24 to give 2-(4-aminophenyl)-7-(2-hydroxyethyloxy)-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 20.

Examples 240-253

The compound obtained in Example 5 and the corresponding starting compounds are treated in the same manner as in Example 6 to give the following compounds as listed in Table 20.

2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-7-(2-phenylethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 240 (1));

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(2-phenylethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 240 (2));

7-benzoylmethyloxy-2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 241 (1));

2-(4-aminophenyl)-7-benzoylmethyloxy-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 241 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-7-(2-nitrobenzyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 242 (1));

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(2-nitrobenzyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 242 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-7-(3-nitrobenzyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 243 (1));

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(3-nitrobenzyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 243 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-7-cyclohexylmethyloxy-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 244 (1));

2-(4-aminophenyl)-7-cyclohexylmethyloxy-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 244 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-7-(methoxycarbonylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 245 (1));

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(methoxycarbonylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 245 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-7-(3,4-dichlorobenzyloxy)-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 246 (1));

2-(4-aminophenyl)-7-(3,4-dichlorobenzyloxy)-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 246 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxy-

carbonyl-7-(4-nitrobenzyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 247 (1));

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(4-nitrobenzyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 247 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-7-(4-phenylbenzyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 248 (1));

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(4-phenylbenzyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 248 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-7-(3-methoxycarbonylbenzyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 249 (1));

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(3-methoxycarbonylbenzyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 249 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-7-(2-fluorobenzyloxy)-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 250 (1));

2-(4-aminophenyl)-7-(2-fluorobenzyloxy)-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 250 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-7-(1-naphthylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-

isoquinolinone (Example 251 (1));

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(1-naphthylmethyl-oxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 251 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxy-carbonyl-7-(2-naphthylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 252 (1));

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(2-naphthylmethyl-oxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 252 (2));

7-allyloxy-2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 253 (1));

7-allyloxy-2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 253 (2));

Example 254

(1) The compound obtained in Example 5 and the corresponding starting compounds are treated in the same manner as in Example 6-(1) to give 2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-7-(4-methoxy-carbonylbenzyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone.

m.p. 197-199°C

(2) The compound thus obtained is treated in the same manner as in Example 21 to give 2-(4-aminophenyl)-7-(4-carboxybenzyloxy)-6-methoxy-3-methoxy-carbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 20.

(3) The compound thus obtained is treated in the same manner as in Example 6-(2) to give 2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(4-methoxycarbonylbenzyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 20.

Example 255

(1) A suspension of the compound obtained in Example 5 (300 mg), 2-bromopyridine (57 μl), copper iodide (113 mg) and potassium carbonate (82 mg) in dimethylformamide (5 ml) is heated with stirring at 80°C for five hours. After the reaction is complete, the reaction mixture is extracted with ethyl acetate. The extract is washed with aqueous ammonia, and further washed with water, dried, and concentrated under reduced pressure. The residue is purified by Chromatotron (solvent; hexane:ethyl acetate = 1:1) to give 2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-7-(2-pyridyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (40 mg) as listed in Table 20.

(2) The compound thus obtained is treated in the same manner as in Example 24 to give 2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(2-pyridyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride as listed in Table 20.

Example 256

(1) The compound obtained in Example 5 and the corresponding starting compounds are treated in the same manner as in Example 218 to give 2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-7-[(1-methyl-4-nitro)pyrrol-2-yl-carbonyloxy]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 20.

(2) The compound thus obtained is treated in the same manner as in Example

6-(2) to give 2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-[(1-methyl-4-nitro)pyrrol-2-yl-carbonyloxy]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 20.

Example 257

(1) The compound obtained in Example 5 (200 mg) is dissolved in dimethylformamide (10 ml), and thereto are added benzoyl chloride (40 μl), triethylamine (48 μl) and 4-dimethylaminopyridine (5 mg), and the mixture is stirred at room temperature overnight. After the reaction is complete, to the mixture is added a saturated aqueous sodium hydrogen carbonate solution, and the mixture is extracted with ethyl acetate. The extract is washed, dried, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; hexane:ethyl acetate = 1:1) to give 7-benzoyloxy-2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 20.

(2) The compound thus obtained is treated in the same manner as in Example 6-(2) to give 2-(4-aminophenyl)-7-benzoyloxy-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 20.

Example 258

(1) The compound obtained in Example 5 and the corresponding starting compounds are treated in the same manner as in Example 218 to give 2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-7-(2-pyrrolylcarbonyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 20, which is used in the subsequent reaction without further purification.

(2) The compound thus obtained is treated in the same manner as in Example

6-(2) to give 2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(2-pyrrolyl-carbonyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 20.

Examples 259-268

The compound obtained in Example 5 and the corresponding starting compounds are treated in the same manner as in Example 7 to give the following compounds as listed in Table 20.

2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxy-carbonyl-7-[2-(2-pyridyl)ethyloxy]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 259 (1));

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-[2-(2-pyridyl)ethyl-oxy]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 259 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxy-carbonyl-4-(3,4,5-trimethoxyphenyl)-7-(3-thienylmethyloxy)-1(2H)-isoquinolin-one (Example 260 (1));

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxy-phenyl)-7-(3-thienylmethyloxy)-1(2H)-isoquinolinone hydrochloride (Example 260 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxy-carbonyl-4-(3,4,5-trimethoxyphenyl)-7-(4-quinolylmethyloxy)-1(2H)-isoquinolinone (Example 261 (1));

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(4-quinolylmethyl-oxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 261 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-7-(3-methylbenzyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 262 (1));

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(3-methylbenzyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 262 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-7-[(2-chloro-5-nitro)benzyloxy]-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 263 (1));

2-(4-aminophenyl)-7-[(2-chloro-5-nitro)benzyloxy]-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 263 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-7-(3-methoxybenzyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 264 (1)), which is used in the subsequent reaction without further purification;

2-(4-aminophenyl)-6-methoxy-7-(3-methoxybenzyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 264 (2));

7-[3-(tert-butoxycarbonylamino)benzyloxy]-2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 265 (1)), which is used in the subsequent reaction without further purification;

7-(3-aminobenzyloxy)-2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride

(Example 265 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-7-cyclopentylmethyloxy-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 266 (1)), which is used in the subsequent reaction without further purification;

2-(4-aminophenyl)-7-cyclopentylmethyloxy-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 266 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-7-[4-(1-tert-butoxycarbonyl)-piperidylmethyloxy]-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 267 (1));

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(4-piperidylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 267 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-7-(2-piperidinoethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 268 (1));

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(2-piperidinoethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 268 (2));

Example 269

(1) A solution of the compound obtained in Example 5 (100 mg) and triethylamine (50 mg) in chloroform (10 ml) is cooled to –10°C, and thereto is added dropwise a solution of triphosgene (49 mg) in chloroform. The mixture is warmed to room temperature, and the mixture is stirred for 30 minutes. To the

mixture is added a solution of N-methylpiperazine (50 mg) and triethylamine (17 mg) in chloroform, and the mixture is further stirred for two hours. After the reaction is complete, the reaction mixture is washed, dried, and concentrated under reduced pressure. The residue is crystallized from diethyl ether to give 2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-7-(4-methylpiperazinylcarbonyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (73 mg) as listed in Table 20.

(2) The compound thus obtained is treated in the same manner as in Example 24 to give 2-(4-aminophenyl)-7-(4-methylpiperazinylcarbonyloxy)-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride as listed in Table 20.

Example 270

(1) The compound obtained in Example 5 and the corresponding starting compounds are treated in the same manner as in Example 269-(1) to give 2-[4-(tert-butoxycarbonylamino)phenyl]-7-diethylaminocarbonyloxy-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 20.

(2) The compound thus obtained is treated in the same manner as in Example 269-(2) to give 2-(4-aminophenyl)-7-diethylaminocarbonyloxy-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 20.

Example 271

(1) The compound obtained in Example 5 and the corresponding starting compounds are treated in the same manner as in Example 269-(1) to give 2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-7-

morpholinocarbonyloxy-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 20.

(2) The compound thus obtained is treated in the same manner as in Example 269-(2) to give 2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-morpholinocarbonyloxy-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 20.

Example 272

(1) The compound obtained in Example 5 and the corresponding starting compounds are treated in the same manner as in Example 6-(1) to give 2-[4-(tert-butoxycarbonylamino)phenyl]-7-cyanomethyl-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone. m.p. 136-138°C.

(2) A solution of the compound thus obtained (310 mg), sodium azide (156 mg) and ammonium chloride (128 mg) in dimethylformamide (30 ml) is heated with stirring at 70°C for 48 hours. To the mixture is added water, and the mixture is extracted with ethyl acetate. The extract is washed, dried, and concentrated under reduced pressure. The residue is crystallized from a mixture of ethyl acetate and diethyl ether to give 2-[4-(tert-butoxycarbonylamino)-phenyl]-6-methoxy-3-methoxycarbonyl-7-(5-tetrazolylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (178 mg) as listed in Table 20.

(3) The compound thus obtained is treated in the same manner as in Example 6-(2) to give 2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(5-tetrazolyl-methyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 20.

Examples 273-275

(1) The compound obtained in Example 6 (1), 236 (1) or 237 (1) is treated

with m-chloroperbenzoic acid to give the following compounds as listed in Table 20.

2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-7-(N-oxo-4-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 273 (1));

2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-7-(N-oxo-3-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 274 (1));

2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-7-(N-oxo-2-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 275 (1));

(2) The compounds thus obtained are treated in the same manner as in Example 6-(2) to give the following compounds as listed in Table 20.

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(N-oxo-4-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 273 (2));

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(N-oxo-3-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 274 (2));

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(N-oxo-2-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 275 (2));

Example 276

(1) The compound obtained in Example 245-(1) is treated in the same manner as in Example 21 to give 2-[4-(tert-butoxycarbonylamino)phenyl]-7-

(carboxymethyloxy)-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone. The compound thus obtained (150 mg) is dissolved in dimethylformamide (5 ml), and thereto is added carbonyl diimidazole (40 mg) under ice-cooling. The mixture is stirred at room temperature for 30 minutes, and thereto is added conc. aqueous ammonia (0.5 ml), and the mixture is stirred at room temperature for one hour. After the reaction is complete, water is added to the mixture, and the mixture is extracted with ethyl acetate. The extract is washed, dried, and concentrated under reduced pressure. The residue is crystallized from diethyl ether to give 2-[4-(tert-butoxycarbonylamino)phenyl]-7-carbamoylmethyloxy-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (141 mg) as listed in Table 20.

(2) The compound thus obtained is treated in the same manner as in Example 24 to give 2-(4-aminophenyl)-7-carbamoylmethyloxy-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 20.

Example 277

(1) The compound obtained in Example 249-(1) is treated in the same manner as in Example 21 to give 2-[4-(tert-butoxycarbonylamino)phenyl]-7-(3-carboxybenzyloxy)-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 20, which is used in the subsequent reaction without further purification.

(2) The compound thus obtained is treated in the same manner as in Example 24 to give 2-(4-aminophenyl)-7-(3-carboxybenzyloxy)-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride as

listed in Table 20.

Examples 278-279

The compound obtained in Example 2 and the corresponding starting compounds are treated in the same manner as in Example 3 to give the following compounds as listed in Table 21.

6-methoxy-3-methoxycarbonyl-2-morpholino-7-(4-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 278);

6-methoxy-3-methoxycarbonyl-2-morpholino-7-(3-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 279);

Example 280

6-Benzyloxy-3-hydroxy-7-methoxy-4-(3,4,5-trimethoxyphenyl)-3-carboxylic acid (the compound obtained in Reference Example 72) and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give 6-benzyloxy-2-[4-(tert-butoxycarbonylamino)phenyl]-7-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 22.

Example 281

The compound obtained in Example 280 is treated in the same manner as in Example 5 to give 2-[4-(tert-butoxycarbonylamino)phenyl]-6-hydroxy-7-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 22.

Examples 282-283

The compounds obtained in Example 280-281 are treated in the same manner as in Example 6-(2) to give the following compounds as listed in Table 22.

2-(4-aminophenyl)-6-benzyloxy-7-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 282);

2-(4-aminophenyl)-6-hydroxy-7-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 283);

Examples 284-291

The compound obtained in Example 281 and the corresponding starting compounds are treated in the same manner as in Example 6 to give the following compounds as listed in Table 22.

2-[4-(tert-butoxycarbonylamino)phenyl]-7-methoxy-3-methoxycarbonyl-6-[2-(2-methoxyethyloxy)ethyloxy]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 284 (1));

2-(4-aminophenyl)-7-methoxy-3-methoxycarbonyl-6-[2-(2-methoxyethyloxy)ethyloxy]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 284 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-6-ethoxy-7-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 285 (1));

2-(4-aminophenyl)-6-ethoxy-7-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 285 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-7-methoxy-3-methoxycarbonyl-6-(2-methoxyethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 286 (1));

2-(4-aminophenyl)-7-methoxy-3-methoxycarbonyl-6-(2-methoxyethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 286 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-6-(2-hydroxyethyloxy)-7-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 287 (1));

2-(4-aminophenyl)-6-(2-hydroxyethyloxy)-7-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 287 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-7-methoxy-3-methoxycarbonyl-6-(4-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 288 (1));

2-(4-aminophenyl)-7-methoxy-3-methoxycarbonyl-6-(4-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 288 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-7-methoxy-3-methoxycarbonyl-6-(3-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 289 (1));

2-(4-aminophenyl)-7-methoxy-3-methoxycarbonyl-6-(3-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 289 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-7-methoxy-3-methoxycarbonyl-6-(2-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 290 (1));

2-(4-aminophenyl)-7-methoxy-3-methoxycarbonyl-6-(2-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 290 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-6-cyclopentyloxy-7-methoxy-

3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 291 (1));

2-(4-aminophenyl)-6-cyclopentyloxy-7-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 291 (2));

Example 292

(1) The compound obtained in Example 281 and the corresponding starting compounds are treated in the same manner as in Example 7-(1) to give 2-[4-(tert-butoxycarbonylamino)phenyl]-7-methoxy-3-methoxycarbonyl-6-[(2-(2-pyridyl)ethyloxy]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 22.

(2) The compound thus obtained is treated in the same manner as in Example 7-(2) to give 2-(4-aminophenyl)-7-methoxy-3-methoxycarbonyl-6-[(2-(2-pyridyl)ethyloxy]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride as listed in Table 22.

Examples 293-294

6,7-Dimethoxy-4-(3,4-methylenedioxyphenyl)isocoumarin-3-carboxylic acid (the compound obtained in Reference Example 65) or 4-(3,4-dichloro-phenyl)-6,7-dimethoxyisocoumarin-3-carboxylic acid (the compound obtained in Reference Example 62), and the corresponding starting compounds are treated in the same manner as in Example 1 or 39 to give the following compounds as listed in Table 23.

6,7-dimethoxy-3-methoxycarbonyl-4-(3,4-methylenedioxyphenyl)-2-phenyl-1(2H)-isoquinolinone (Example 293);

4-(3,4-dichlorophenyl)-6,7-dimethoxy-3-methoxycarbonyl-2-phenyl-

1(2H)-isoquinolinone (Example 294);

Example 295

The compound obtained in Example 202 is treated in the same manner as in Example 40 to give 2-(4-aminophenyl)-4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-1(2H)-isoquinolinone hydrochloride as listed in Table 24.

Example 296

4-(3-Bromo-4,5-dimethoxyphenyl)-6,7-dimethoxyisocoumarin-3-carboxylic acid (the compound obtained in Reference Example 60) and the corresponding starting compounds are treated in the same manner as in Example 1 or 39 to give 4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-2-(6-1H-indazolyl)-3-methoxycarbonyl-1(2H)-isoquinolinone as listed in Table 24.

Example 297

3-Hydroxy-4-(3,4,5-trimethoxyphenyl)-3,4-dihydroisocoumarin-3-carboxylic acid (the compound obtained in Reference Example 75) and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give 2-(1-indolyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 24.

Example 298

To a solution of the compound obtained in Example 67 (5.60 g) in methylene chloride (15 ml) is added trifluoroacetic acid (15 ml), and the mixture is allowed to stand at room temperature for three hours. After the reaction is complete, the reaction mixture is concentrated under reduced pressure. The resulting residue is dissolved in ethyl acetate, and extracted. The extract is washed, dried, and concentrated under reduced pressure. The resulting residue

is crystallized from ethyl acetate to give 3-methoxycarbonyl-2-(trifluoroacetyl-amino)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 24.

Example 299

4-(3,5-Dibromo-4-methoxyphenyl)-6,7-dimethoxy-3-hydroxy-3,4-dihydroisocoumarin-3-carboxylic acid (the compound obtained in Reference Example 86) and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give 4-(3,5-dibromo-4-methoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-2-phenyl-1(2H)-isoquinolinone as listed in Table 24.

Examples 300-308

The compound obtained in Example 8-(2) and the corresponding starting compounds are treated in the same manner as in Example 9 to give the following compounds as listed in Table 25.

2-(4-aminophenyl)-7-(4-aminobenzyloxy)-6-methoxy-3-methoxy-carbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 300);

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(3,4-methylene-dioxybenzyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydro-chloride (Example 301);

2-(4-aminophenyl)-7-(2,4-dimethoxybenzyloxy)-6-methoxy-3-methoxy-carbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 302);

2-(4-aminophenyl)-7-(2,5-dimethoxybenzyloxy)-6-methoxy-3-methoxy-carbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 303);

2-(4-aminophenyl)-7-(3,5-dimethoxybenzyloxy)-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 304);

2-(4-aminophenyl)-7-(3,4-dimethoxybenzyloxy)-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 305);

2-(4-aminophenyl)-7-(2,3-dimethoxybenzyloxy)-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 306);

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(2-methoxybenzyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 307);

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(4-methoxybenzyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 308);

Examples 309-316

The compound obtained in Example 223 and the corresponding starting compounds are treated in the same manner as in Example 6 or 7 to give the following compounds as listed in Table 26.

2-(4-aminophenyl)-7-(2-benzimidazolylmethyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 309);

2-(4-aminophenyl)-3-methoxycarbonyl-7-(4-methylphenylsulfonyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 310);

2-[4-(tert-butoxycarbonylamino)phenyl]-3-methoxycarbonyl-7-(4-

pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 311 (1));

2-(4-aminophenyl)-3-methoxycarbonyl-7-(4-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 311 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-3-methoxycarbonyl-7-(3-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 312 (1));

2-(4-aminophenyl)-3-methoxycarbonyl-7-(3-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 312 (2));

2-[4-(tert-butoxycarbonylamino)phenyl]-3-methoxycarbonyl-7-(2-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 313 (1));

2-(4-aminophenyl)-3-methoxycarbonyl-7-(2-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 313 (2));

2-(4-aminophenyl)-3-methoxycarbonyl-7-(4-nitrobenzyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 314);

2-(4-aminophenyl)-3-methoxycarbonyl-7-(3-nitrobenzyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 315);

2-(4-aminophenyl)-3-methoxycarbonyl-7-(2-nitrobenzyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 316);

Example 317

7-Benzyloxy-4-(4-bromo-3,5-dimethoxyphenyl)-6-methoxy-3,4-dihydro-isocoumarin-3-carboxylic acid (the compound obtained in Reference Example 102) and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give 7-benzyloxy-4-(4-bromo-3,5-dimethoxyphenyl)-

2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-1(2H)-isoquinolinone as listed in Table 27.

Example 318

The compound obtained in Example 317 is treated in the same manner as in Example 24 to give 2-(4-aminophenyl)-7-benzyloxy-4-(4-bromo-3,5-dimethoxyphenyl)-6-methoxy-3-methoxycarbonyl-1(2H)-isoquinolinone hydrochloride as listed in Table 27.

Example 319

(1) The compound obtained in Example 317 (3.66 g) is dissolved in 1,4-dioxane (45 ml), and thereto are added conc. hydrochloric acid (50 ml) and methanol (5 ml). The mixture is heated with stirring at 90°C for 1.5 hour. To the mixture is added gradually a 2M aqueous sodium hydroxide solution (200 ml) under ice-cooling, and the mixture is neutralized with a saturated aqueous sodium hydrogen carbonate solution. The mixture is extracted with ethyl acetate, and the extract is washed, dried, and concentrated under reduced pressure. The residue is crystallized from diethyl ether to give 2-(4-amino-phenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-7-hydroxy-6-methoxy-3-methoxy-carbonyl-1(2H)-isoquinolinone (2.54 g) as listed in Table 27.

(2) The compound thus obtained is reacted in the same manner as in Example 9-(3) to give 2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-7-hydroxy-6-methoxy-3-methoxycarbonyl-1(2H)-isoquinolinone hydrochloride as listed in Table 27.

Example 320

A mixture of the compound obtained in Example 319-(1) (400 mg), 4-picolyl chloride hydrochloride (120 mg) and potassium carbonate (252 mg) in

dimethylformamide (15 ml) is heated with stirring at 60°C for three hours. To the mixture is added water, and the mixture is extracted with ethyl acetate. The ethyl acetate layer is washed, dried, and concentrated under reduced pressure. The residue is crystallized from ethyl acetate, and the resulting crystals are dissolved in a mixture of chloroform (20 ml) and methanol (5 ml). To the mixture is added a 4M solution of hydrogen chloride in ethyl acetate (5 ml), and the mixture is crystallized from diethyl ether to give 2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-6-methoxy-3-methoxycarbonyl-7-(4-pyridylmethyloxy)-1(2H)-isoquinolinone dihydrochloride (328 mg) as listed in Table 27.

Examples 321-323

The compound obtained in Example 319-(1) and the corresponding starting compounds are treated in the same manner as in Example 320 to give the following compounds as listed in Table 27.

2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-6-methoxy-3-methoxycarbonyl-7-(3-pyridylmethyloxy)-1(2H)-isoquinolinone dihydrochloride (Example 321);

2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-6-methoxy-3-methoxycarbonyl-7-(2-pyridylmethyloxy)-1(2H)-isoquinolinone dihydrochloride (Example 322);

2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-6-methoxy-3-methoxycarbonyl-7-(2-quinolylmethyloxy)-1(2H)-isoquinolinone dihydrochloride (Example 323);

Example 324

7-Benzyloxy-4-(3,4,5-trimethoxyphenyl)isocoumarin-3-carboxylic acid (the compound obtained in Reference Example 67) and the corresponding

starting compounds are treated in the same manner as in Example 1 or 39 to give 7-benzyloxy-3-methoxycarbonyl-2-morpholino-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 28.

Example 325

The compound obtained in Example 324 is treated in the same manner as in Example 2 to give 7-hydroxy-3-methoxycarbonyl-2-morpholino-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 28.

Examples 326-328

The compound obtained in Example 325 and the corresponding starting compounds are treated in the same manner as in Example 6 or 7 to give the following compounds as listed in Table 28.

3-methoxycarbonyl-2-morpholino-7-(2-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 326);

3-methoxycarbonyl-2-morpholino-7-(3-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 327);

3-methoxycarbonyl-2-morpholino-7-(4-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 328);

Examples 329-333

The compound obtained in Example 5 and the corresponding starting compounds are treated in the same manner as in Example 6 or 7 to give the following compounds as listed in Table 29.

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-[(4-methyl)-imidazol-5-yl-methyloxy]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 329);

2-[4-(tert-butoxycarbonylamino)phenyl]-7-cyclopropylmethyloxy-6-

methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 330-(1));

2-(4-aminophenyl)-7-cyclopropylmethyloxy-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 330-(2));

2-(4-aminophenyl)-7-[(2-hydroxymethyl)pyridin-6-yl-methyloxy]-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 331);

2-(4-aminophenyl)-7-(3,5-diaminobenzyloxy)-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone trihydrochloride (Example 332);

2-(4-aminophenyl)-7-(2-benzimidazolylmethyloxy)-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone trihydrochloride (Example 333);

Example 334

3-Hydroxy-4-(3,4,5-trimethoxyphenyl)-3,4-dihydroisocoumarin-3-carboxylic acid (the compound obtained in Reference Example 75) and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give 2-[4-(2,6-dioxo)piperidyl]-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 30.

Example 335

8-Benzyloxy-3-hydroxy-4-(3,4,5-trimethoxyphenyl)-3,4-dihydroisocoumarin-3-carboxylic acid (the compound obtained in Reference Example 79) and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give 8-benzyloxy-2-[4-(tert-butoxycarbonylamino)-

phenyl]-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 30.

Example 336

A solution of the compound obtained in Example 335 (53 mg) in chloroform (4 ml) is cooled to 0°C, and thereto is added a 4M solution of hydrogen chloride in ethyl acetate (2 ml). The mixture is stirred at 0°C for two hours, and thereto is added a saturated aqueous sodium hydrogen carbonate solution, and the mixture is extracted with ethyl acetate. The extract is washed, dried, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; hexane:ethyl acetate = 1:2) to give 2-(4-aminophenyl)-8-benzyloxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (20 mg) as listed in Table 30.

Example 337

The compound obtained in Example 336 is treated in the same manner as in Example 24 to give 2-(4-aminophenyl)-8-hydroxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 30.

Example 338

7-Benzyloxy-4-(4-bromo-3,5-dimethoxyphenyl)-3-hydroxy-3,4-dihydro-isocoumarin-3-carboxylic acid (the compound obtained in Reference Example 104) and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give 7-benzyloxy-2-[4-(tert-butoxycarbonylamino)-phenyl]-4-(4-bromo-3,5-dimethoxyphenyl)-3-methoxycarbonyl-1(2H)-isoquinolinone as listed in Table 31.

Example 339

The compound obtained in Example 338 is treated in the same manner as in Example 24 to give 2-(4-aminophenyl)-7-benzyloxy-4-(4-bromo-3,5-dimethoxyphenyl)-3-methoxycarbonyl-1(2H)-isoquinolinone hydrochloride as listed in Table 31.

Example 340

(1) The compound obtained in Example 338 is treated in the same manner as in Example 319-(1) to give 2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-7-hydroxy-3-methoxycarbonyl-1(2H)-isoquinolinone as listed in Table 31.

(2) The compound thus obtained is treated in the same manner as in Example 319-(2) to give 2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-7-hydroxy-3-methoxycarbonyl-1(2H)-isoquinolinone hydrochloride as listed in Table 31.

Example 341

7-Benzyloxy-3-hydroxy-4-(3,4,5-trimethoxyphenyl)-3,4-dihydroisocoumarin-3-carboxylic acid (the compound obtained in Reference Example 73) and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give 7-benzyloxy-3-methoxycarbonyl-2-phenyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 32.

Example 342

The compound obtained in Example 341 is treated in the same manner as in Example 2 to give 7-hydroxy-3-methoxycarbonyl-2-phenyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 32.

Examples 343-347

The compound obtained in Example 342 and the corresponding starting

compounds are treated in the same manner as in Example 6 or 7 to give the following compounds as listed in Table 32.

3-methoxycarbonyl-2-phenyl-7-(2-quinolylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 343);

3-methoxycarbonyl-2-phenyl-7-(4-quinolylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 344);

3-methoxycarbonyl-2-phenyl-7-(4-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 345);

3-methoxycarbonyl-2-phenyl-7-(3-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 346);

3-methoxycarbonyl-2-phenyl-7-(2-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 347);

Example 348

The corresponding starting compounds are treated in the same manner as in Example 3 to give 3-methoxycarbonyl-2-morpholino-7-(2-quinolylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 33.

Examples 349-352

The corresponding starting compounds are treated in the same manner as in Example 9 to give the following compounds as listed in Table 34.

2-(4-aminophenyl)-7-(3-dimethylaminobenzyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 349);

2-(4-aminophenyl)-3-methoxycarbonyl-7-pyrazinylmethyloxy-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 350);

2-(4-aminophenyl)-7-(3,5-dimethoxybenzyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 351);

2-(4-aminophenyl)-7-(2,5-dimethoxybenzyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 352);

Example 353

7-Benzyloxy-4-(4-chloro-3,5-dimethoxyphenyl)-3-hydroxy-3,4-dihydro-isocoumarin-3-carboxylic acid (the compound obtained in Reference Example 105) and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give 7-benzyloxy-2-[4-(tert-butoxycarbonylamino)-phenyl]-4-(4-chloro-3,5-dimethoxyphenyl)-3-metoxycarbonyl-1(2H)-isoquinolinone, which is further treated in the same manner as in Example 24 to give 2-(4-aminophenyl)-7-benzyloxy-4-(4-chloro-3,5-dimethoxyphenyl)-3-metoxycarbonyl-1(2H)-isoquinolinone hydrochloride as listed in Table 35.

Example 354

The compound obtained in Example 353 is treated in the same manner as in Example 319-(1) to give 2-(4-aminophenyl)-4-(4-chloro-3,5-dimethoxy-phenyl)-7-hydroxy-3-methoxycarbonyl-1(2H)-isoquinolinone as listed in Table 35.

Examples 355-358

The compound obtained in Example 354 and the corresponding starting compounds are treated in the same manner as in Example 320 or Example 9 (1) and (3), to give the following compounds as listed in Table 35.

2-(4-aminophenyl)-4-(4-chloro-3,5-dimethoxyphenyl)-3-methoxy-carbonyl-7-(2-pyridylmethyloxy)-1(2H)-isoquinolinone dihydrochloride (Example 355);

2-(4-aminophenyl)-4-(4-chloro-3,5-dimethoxyphenyl)-3-methoxycarbonyl-7-(3-pyridylmethyloxy)-1(2H)-isoquinolinone dihydrochloride (Example 356);

2-(4-aminophenyl)-4-(4-chloro-3,5-dimethoxyphenyl)-3-methoxycarbonyl-7-(4-pyridylmethyloxy)-1(2H)-isoquinolinone dihydrochloride (Example 357);

2-(4-aminophenyl)-4-(4-chloro-3,5-dimethoxyphenyl)-3-methoxycarbonyl-7-(2-quinolylmethyloxy)-1(2H)-isoquinolinone dihydrochloride (Example 358);

Examples 359-364

The compound obtained in Example 340 (1) and the corresponding starting compounds are treated in the same manner as in Example 320, or Example 9 (1) and (3), to give the following compounds as listed in Table 35.

2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-3-methoxycarbonyl-7-(2-pyridylmethyloxy)-1(2H)-isoquinolinone dihydrochloride (Example 359);

2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-3-methoxycarbonyl-7-(3-pyridylmethyloxy)-1(2H)-isoquinolinone dihydrochloride (Example 360);

2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-3-methoxycarbonyl-7-(4-pyridylmethyloxy)-1(2H)-isoquinolinone dihydrochloride (Example 361);

2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-3-methoxycarbonyl-7-(2-quinolylmethyloxy)-1(2H)-isoquinolinone dihydrochloride (Example 362);

2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-7-(3,5-dimethoxybenzyloxy)-3-methoxycarbonyl-1(2H)-isoquinolinone hydrochloride (Example 363);

7-(3-aminobenzyloxy)-2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-3-methoxycarbonyl-1(2H)-isoquinolinone dihydrochloride (Example 364);

Examples 365-366

The compound obtained in Example 319 (1) and the corresponding starting compounds are treated in the same manner as in Example 9 (1) and (3) to give the following compounds as listed in Table 37.

2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-7-(3,5-dimethoxybenzyloxy)-6-methoxy-3-methoxycarbonyl-1(2H)-isoquinolinone hydrochloride (Example 365);

2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-7-(2,5-dimethoxybenzyloxy)-6-methoxy-3-methoxycarbonyl-1(2H)-isoquinolinone hydrochloride (Example 366);

Example 367

The compound obtained in Example 319 (1) and the corresponding starting compounds are treated in the same manner as in Example 320 to give 2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-7-cyanomethyloxy-6-methoxy-3-methoxycarbonyl-1(2H)-isoquinolinone hydrochloride as listed in Table 37.

Example 368

The compound obtained in Example 319 (1) and the corresponding starting compounds are treated in the same manner as in Example 9 (1) and (3)

to give 2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-7-(1-isoquinolylmethyloxy)-6-methoxy-3-methoxycarbonyl-1(2H)-isoquinolinone dihydrochloride as listed in Table 37.

Example 369

A suspension of the compound obtained in Example 224 in chloroform is neutralized with a 2M aqueous sodium hydroxide solution under ice-cooling, and the mixture is extracted with ethyl acetate. The extract is washed, dried, and concentrated under reduced pressure. The residue is dissolved in a small amount of ethyl acetate, and the mixture is crystallized from diethyl ether to give 2-(4-aminophenyl)-7-hydroxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 38.

Example 370

The compound obtained in Example 369 is treated in the same manner as in Example 8-(2) to give 2-[4-(9-fluorenylmethyloxycarbonylamino)phenyl]-7-hydroxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 38.

Examples 371-374

The compound obtained in Example 223 and the corresponding starting compounds are treated in the same manner as in Example 6 or 7 to give the following compounds as listed in Table 38.

2-(4-aminophenyl)-7-(3,5-diaminobenzyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone trihydrochloride (Example 371);

2-(4-aminophenyl)-7-(6-hydroxymethyl-2-pyridylmethyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 372);

2-[4-(tert-butoxycarbonylamino)phenyl]-7-(4-methoxycarbonylbenzyl-oxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 373-(1));

2-(4-aminophenyl)-7-(4-methoxycarbonylbenzyloxy)-3-methoxy-carbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 373-(2));

2-[4-(tert-butoxycarbonylamino)phenyl]-7-(3-methoxycarbonylbenzyl-oxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 374);

Examples 375-376

The compound obtained in Example 373-(1) or 374 is treated in the same manner as in Example 21-(1) and Example 6-(2) to give the following compounds as listed in Table 38.

2-[4-(tert-butoxycarbonylamino)phenyl]-7-(4-carboxybenzyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 375-(1));

2-(4-aminophenyl)-7-(4-carboxybenzyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 375-(2));

2-[4-(tert-butoxycarbonylamino)phenyl]-7-(3-carboxybenzyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 376-(1));

2-(4-aminophenyl)-7-(3-carboxybenzyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 376-(2));

Examples 377-378

The compound obtained in Example 375-(1) or 376-(1), and the corresponding starting compounds are treated in the same manner as in Example 129 and 6 (2) to give the following compounds as listed in Table 39.

2-(4-aminophenyl)-3-methoxycarbonyl-7-[4-(4-methylpiperazinyl-carbonyl)benzyloxy]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 377);

2-(4-aminophenyl)-3-methoxycarbonyl-7-[3-(4-methylpiperazinyl-carbonyl)benzyloxy]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 378);

Examples 379-382

The compound obtained in Example 369 and the corresponding starting compounds are treated in the same manner as in Example 9-(1), and the product thus obtained is further treated in the same manner as in Example 9-(3) to give the following compounds as listed in Table 39.

2-(4-aminophenyl)-3-methoxycarbonyl-7-[3-(methylamino)benzyloxy]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 379);

2-(4-aminophenyl)-7-(2-hydroxymethylbenzyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 380);

2-(4-aminophenyl)-7-(3-hydroxymethylbenzyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 381);

2-(4-aminophenyl)-7-(4-hydroxymethylbenzyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 382);

Example 383

The compound obtained in Example 312-(2) is treated in the same manner as in Example 69 to give 2-[4-(acetylamino)phenyl]-3-methoxycarbonyl-7-(2-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 40.

Example 384

(1) The compound obtained in Example 313-(1) is treated in the same manner as in Example 273 to give 2-[4-(tert-butoxycarbonylamino)phenyl]-3-methoxycarbonyl-7-(N-oxo-2-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 40.

(2) The compound thus obtained is treated in the same manner as in Example 6-(2), and the product thus obtained is further treated in the same manner as in Example 369 to give 2-(4-aminophenyl)-3-methoxycarbonyl-7-(N-oxo-2-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 40.

Examples 385-386

The compound obtained in Example 325 and the corresponding starting compounds are treated in the same manner as in Example 6 or 7 to give the following compounds as listed in Table 40.

7-(3-aminobenzyloxy)-3-methoxycarbonyl-2-morpholino-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 385);

7-(2-benzimidazolylmethyloxy)-3-methoxycarbonyl-2-morpholino-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (Example 386);

Example 387

The compound obtained in Example 335 is treated in the same manner as in Example 8-(1) to give 2-(4-aminophenyl)-8-hydroxy-3-methoxycarbonyl-4-

(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone as listed in Table 41.

Examples 388-392

The compound obtained in Example 387 is treated in the same manner as in Example 6 to give the following compounds as listed in Table 41.

2-(4-aminophenyl)-3-methoxycarbonyl-8-(2-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 388);

2-(4-aminophenyl)-3-methoxycarbonyl-8-(3-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 389);

2-(4-aminophenyl)-3-methoxycarbonyl-8-(4-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 390);

2-(4-aminophenyl)-3-methoxycarbonyl-8-(2-quinolylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride (Example 391);

2-(4-aminophenyl)-3-methoxycarbonyl-8-(phenylethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride (Example 392);

Example 393

The compound obtained in Example 369 and the corresponding starting compounds are treated in the same manner as in Example 7 to give 2-(4-aminophenyl)-7-(4-imidazolylmethyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dihydrochloride as listed in Table 41.

Example 394

The compound obtained in Example 382 (300 mg) and triethylamine (0.36 ml) is dissolved in dichloromethane (5 ml), and methanesulfonyl chloride (0.084 ml) is added dropwise thereto under ice-cooling. After 12 hours, the reaction mixture is poured into water, and extracted with dichloromethane. The extract is washed, dried, and concentrated under reduced pressure. The

residue is dissolved in dimethylformamide (5 ml) and thereto is added sodium bisformylamide (285 mg), and then the mixture is stirred for 12 hours at room temperature. The reaction mixture is poured into water, and extracted with ethyl acetate. The extract is washed, dried, and concentrated under reduced pressure. To the residue are added ethanol (5 ml) and conc. hydrochloric acid solution (1 ml), and the mixture is stirred for 12 hours at room temperature. The reaction mixture is poured into a saturated aqueous sodium hydrogen carbonate solution, and extracted with chloroform. The extract is washed, dried, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; chloroform:acetone = 3:1) to give 7-(4-amino-methylbenzyloxy)-2-(4-methanesulfonylaminophenyl)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (108 mg) as listed in Table 41.

Examples 395-398

The compound obtained in Example 354 and the corresponding starting compounds are treated in the same manner as in Example 320 or 9-(1), and the product thus obtained is further treated in the same manner as in Example 9-(3) to give the following compounds as listed in Table 42.

2-(4-aminophenyl)-7-(2-benzimidazolylmethyloxy)-4-(4-chloro-3,5-dimethoxyphenyl)-3-methoxycarbonyl-1(2H)-isoquinolinone dihydrochloride (Example 395);

2-(4-aminophenyl)-4-(4-chloro-3,5-dimethoxyphenyl)-7-(3,5-dimethoxy-benzyloxy)-3-methoxycarbonyl-1(2H)-isoquinolinone hydrochloride (Example 396);

2-(4-aminophenyl)-4-(4-chloro-3,5-dimethoxyphenyl)-7-(6-hydroxy-methyl-2-pyridylmethyloxy)-3-methoxycarbonyl-1(2H)-isoquinolinone dihydro-

chloride (Example 397);

2-(4-aminophenyl)-4-(4-chloro-3,5-dimethoxyphenyl)-3-methoxycarbonyl-7-pyrazinylmethyloxy-1(2H)-isoquinolinone dihydrochloride (Example 398);

Example 399

The compound obtained in Example 319-(1) and the corresponding starting compounds are treated in the same manner as in Example 9-(1), and the product thus obtained is further treated in the same manner as in Example 9-(3) to give 2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-7-(2-furylmethyloxy)-6-methoxy-3-methoxycarbonyl-1(2H)-isoquinolinone hydrochloride as listed in Table 43.

Example 400

7-Benzyloxy-3-hydroxy-6-methoxy-4-(3,5-dimethoxy)-4-methylphenyl)-3,4-dihydroisocoumarin-3-carboxylic acid (the compound obtained in Reference Example 103) is treated in the same manner as in Example 4 to give 7-benzyloxy-2-[4-(tert-butoxycarbonylamino)phenyl]-6-methoxy-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 43.

Examples 401

The compound obtained in Example 400 is treated in the same manner as in Example 6-(2) to give 2-(4-aminophenyl)-7-benzyloxy-6-methoxy-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 43.

Example 402

The compound obtained in Example 400 is treated in the same manner as

in Example 5 to give 2-[4-(tert-butoxycarbonylamino)phenyl]-7-hydroxy-6-methoxy-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-1(2H)-isoquinolinone as listed in Table 43.

Example 403

The compound obtained in Example 402 is treated in the same manner as in Example 6-(2) to give 2-(4-aminophenyl)-7-hydroxy-6-methoxy-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 43.

Examples 404-407

The compound obtained in Example 402 and the corresponding starting compounds are treated in the same manner as in Example 6 to give the following compounds as listed in Table 43.

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-7-(4-pyridylmethyloxy)-1(2H)-isoquinolinone dihydrochloride (Examples 404);

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-7-(3-pyridylmethyloxy)-1(2H)-isoquinolinone dihydrochloride (Examples 405);

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-7-(2-pyridylmethyloxy)-1(2H)-isoquinolinone dihydrochloride (Examples 406);

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-7-(2-quinolylmethyloxy)-1(2H)-isoquinolinone dihydrochloride (Examples 407);

Example 408

7-Benzyloxy-3-hydroxy-4-(3,5-dimethoxyphenyl-4-methylphenyl)-3,4-dihydroisocoumarin-3-carboxylic acid (the compound obtained in Reference Example 106) is treated in the same manner as in Example 4 to give 7-benzyloxy-2-[4-(tert-butoxycarbonylamino)phenyl]-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-1(2H)-isoquinolinone as listed in Table 44.

Example 409

The compound obtained in Example 408 is treated in the same manner as in Example 6-(2) to give 2-(4-aminophenyl)-7-benzyloxy-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 44.

Example 410

The compound obtained in Example 408 is treated in the same manner as in Example 5 to give 2-[4-(tert-butoxycarbonylamino)phenyl]-7-hydroxy-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-1(2H)-isoquinolinone as listed in Table 44.

Example 411

The compound obtained in Example 410 is treated in the same manner as in Example 6-(2) to give 2-(4-aminophenyl)-7-hydroxy-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-1(2H)-isoquinolinone hydrochloride as listed in Table 44.

Examples 412-421

The compound obtained in Example 410 and the corresponding starting compounds are treated in the same manner as in Example 6 or 7 to give the following compounds as listed in Tables 44 and 45.

2-(4-aminophenyl)-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methyl-

phenyl)-7-(4-pyridylmethyloxy)-1(2H)-isoquinolinone dihydrochloride (Examples 412);

2-(4-aminophenyl)-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-7-(3-pyridylmethyloxy)-1(2H)-isoquinolinone dihydrochloride (Examples 413);

2-(4-aminophenyl)-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-7-(2-pyridylmethyloxy)-1(2H)-isoquinolinone dihydrochloride (Examples 414);

2-(4-aminophenyl)-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-7-(2-quinolylmethyloxy)-1(2H)-isoquinolinone dihydrochloride (Examples 415);

2-(4-aminophenyl)-7-(1-isoquinolylmethyloxy)-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-1(2H)-isoquinolinone dihydrochloride (Examples 416);

2-(4-aminophenyl)-7-(3,5-diaminobenzyloxy)-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-1(2H)-isoquinolinone trihydrochloride (Examples 417);

2-(4-aminophenyl)-7-(6-hydroxymethyl-2-pyridylmethyloxy)-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-1(2H)-isoquinolinone dihydrochloride (Examples 418);

2-(4-aminophenyl)-7-(3-methylaminobenzyloxy)-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-1(2H)-isoquinolinone dihydrochloride (Examples 419);

2-(4-aminophenyl)-7-(2-hydroxymethylbenzyloxy)-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-1(2H)-isoquinolinone hydrochloride

(Examples 420);

2-(4-aminophenyl)-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methyl-phenyl)-7-(2-pyrazinylmethyloxy)-1(2H)-isoquinolinone dihydrochloride (Examples 421);

Example 422

(1) To a solution of the compound obtained in Example 311-(2) (12.2 g) in chloroform (200 ml) is added a saturated aqueous sodium hydrogen carbonate solution, and the mixture is stirred for one hour. The chloroform layer is separated, dried, and concentrated under reduced pressure. The residue is crystallized from ethyl acetate to give 2-(4-aminophenyl)-3-methoxycarbonyl-7-(4-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone (10.8 g) a listed in Table 46.

(2) The compound thus obtained (2.00 g) is dissolved in ethanol (150 ml) under warming at 80°C, and thereto is added dropwise a 1M aqueous sulfuric acid solution (3.53 ml). Then, the mixture is cooled to room temperature, and stirred overnight. The precipitated crystals are collected by filtration, and washed with cooled ethanol to give 2-(4-aminophenyl)-3-methoxycarbonyl-7-(4-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone sulfate (2.12 g) as listed in Table 46.

Example 423

The compound obtained in Example 422-(1) (2.00 g) is dissolved in ethanol (150 ml) under warming at 80°C, and thereto is added methanesulfonic acid (0.48 ml). Then, the mixture is cooled to room temperature and stirred for three hours. The precipitated crystals are collected by filtration, and washed with cooled ethanol to give 2-(4-aminophenyl)-3-methoxycarbonyl-7-(4-

pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dimethanesulfonate (2.65 g) as listed in Table 46.

Examples 424-425

The compound obtained in Example 313-(2) is treated in the same manner as in Example 422 or 423 to give the following compounds as listed in Table 46.

2-(4-aminophenyl)-3-methoxycarbonyl-7-(2-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone sulfate (Example 424);

2-(4-aminophenyl)-3-methoxycarbonyl-7-(2-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone dimethanesulfonate (Example 425);

Example 426

The compound obtained in Reference Example 80 and the corresponding starting compounds are treated in the same manner as in Example 99-(1) to give 4-(3-bromo-4,5-dimethoxyphenyl)-3-carboxy-6,7-dimethoxy-1(2H)-isoquinolinone as listed in Table 47.

Example 427

The compound obtained in Example 429 and the corresponding starting compounds are treated in the same manner as in Example 10-(2) to give 4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-3-methoxycarbonyl-1(2H)-isoquinolinone as listed in Table 47.

Example 428

(1) The compound obtained in Reference Example 107-(5) and the corresponding starting compounds are treated in the same manner as in Example 4 or 31 to give 7-benzyloxy-2-[4-(tert-butoxycarbonylamino)phenyl]-4-(3,4-dimethoxy-5-methoxymethoxyphenyl)-3-methoxycarbonyl-1(2H)-isoquinolin-

one.

(2) The compound thus obtained (540 mg) is treated in the same manner as in Example 5 or 6-(1) to give 2-[4-(tert-butoxycarbonylamino)phenyl]-4-(3,4-dimethoxy-5-methoxymethoxyphenyl)-3-methoxycarbonyl-7-(2-pyridyl-methyloxy)-1(2H)-isoquinolinone.

(3) To a solution of the compound thus obtained in chloroform is added a 4M solution of hydrogen chloride in ethyl acetate, and the mixture is stirred for one hour at room temperature. Ethanol is added thereto, and then the mixture is stirred for three hours at 40°C. The mixture is concentrated under reduced pressure, and ethyl acetate is added thereto. The precipitated crystals are collected by filtration to give 2-(4-aminophenyl)-4-(3,4-dimethoxyphenyl-5-hydroxy)-3-methoxycarbonyl-7-(2-pyridylmethyloxy)-1(2H)-isoquinolinone dihydrochloride as listed in Table 48.

Example 429

To the compound obtained in Example 313-(2) (1.70 g) are added dioxane (30 ml) and conc. hydrochloric acid solution (30 ml), and the mixture is heated under reflux overnight. The reaction mixture is evaporated to remove dioxane, and the residual solution is neutralized with a 2M aqueous sodium hydroxide solution. The mixture is extracted with ethyl acetate, and the extract is washed, dried, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; chloroform:acetone = 3:2) to give 2-(4-aminophenyl)-4-(3,5-dimethoxy-4-hydroxyphenyl)-3-methoxy-carbonyl-7-(2-pyridylmethyloxy)-1(2H)-isoquinolinone (920 mg) as listed in Table 48.

Reference Example 1

2-Bromo-4,5-dimethoxybenzaldehyde dimethyl acetal (74.0 g) is dissolved in tetrahydrofuran (400 ml), and the mixture is cooled to –78°C under nitrogen atmosphere. To the mixture is added dropwise and gradually a 1.6M n-butyl lithium (191 ml), and then the mixture is stirred for 15 minutes. To the mixture is added dropwise a solution of N,N-dimethyl-3,4,5-trimethoxy-benzamide (61 g) in tetrahydrofuran, and the mixture is gradually warmed to –45°C. The reaction mixture is poured into water, and the mixture is extracted with ethyl acetate. The extract is washed with water and a saturated aqueous sodium chloride solution, dried, and concentrated under reduced pressure. The precipitated crystals are collected by filtration with diethyl ether to give 3,4-dimethoxy-6-(3,4,5-trimethoxybenzoyl)benzaldehyde dimethyl acetal (90.0 g) as listed in Table 49.

Reference Examples 2-8

N,N-Dimethyl-3,4,5-trimethoxybenzamide and the corresponding bromobenzaldehyde dimethyl acetal are treated in the same manner as in Reference Example 1 to give the compounds as listed in Table 49.

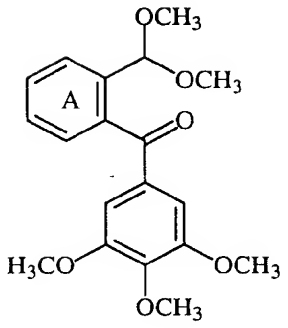
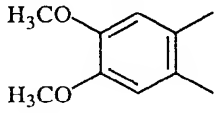
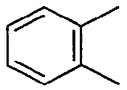
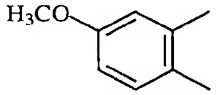
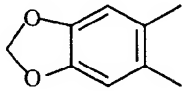
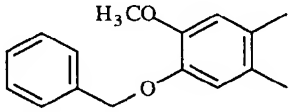
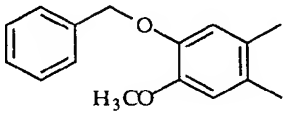
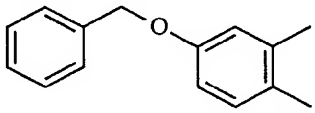
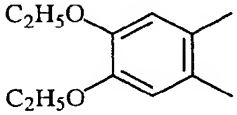


Table 49

Ref. Ex. No.	Ring A	Physicochemical properties
1		m.p. 146-148°C
2		m.p. 87-89°C
3		m.p. 129-131°C
4		m.p. 121-123°C
5		Oil
6		not purified
7		m.p. 230-231°C
8		m.p. 80-82°C

Reference Example 9

2-Bromo-4,5-dimethoxybenzaldehyde dimethyl acetal (5.68 g) is dissolved in tetrahydrofuran (20 ml), and the mixture is cooled to –60°C. To the mixture is added n-butyl lithium (12.8 ml) over a period of 30 minutes. To the mixture is added dropwise a solution of 4-bromo-3,5-dimethoxybenzaldehyde (4.78 g) in tetrahydrofuran over a period of 30 minutes. Acetic acid (1.06 ml) is added to the reaction mixture, and the mixture is poured into water. The resultant mixture is extracted with ethyl acetate. The extract is washed, dried, and concentrated under reduced pressure to give an alcohol compound (9.02 g) as an oily product. The alcohol compound thus obtained is dissolved in toluene (30 ml), and thereto is added solid manganese dioxide (26 g) in portions. The suspension is warmed to 80°C, and five hours thereafter, the insoluble materials are removed by filtration. The filtrate is concentrated under reduced pressure, and the precipitated crystals are collected by filtration to give 2-(4-bromo-3,5-dimethoxybenzoyl)-4,5-dimethoxybenzaldehyde dimethyl acetal (3.68 g) as listed in Table 50.

Reference Examples 10-13

The corresponding starting compounds are treated in the same manner as in Reference Example 9 to give the compounds as listed in Table 50.

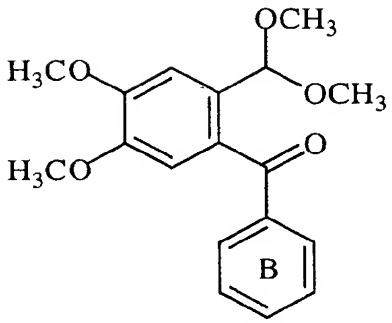
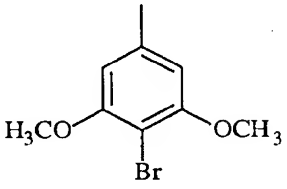
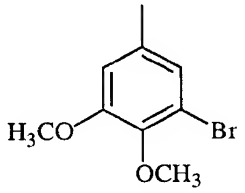
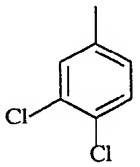
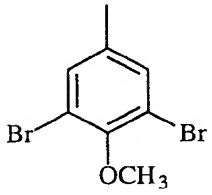
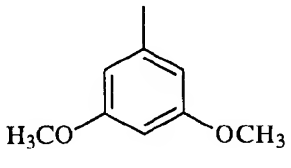


Table 50

Ref. Ex. No.	Ring B	Physicochemical properties
9		m.p. 170-172°C
10		Oil
11		Oil
12		Oil
13		Oil

Reference Example 14

4,5-Dimethoxy-2-(3,4,5-trimethoxybenzoyl)benzaldehyde dimethyl acetal (1.0 g) is dissolved with heating in a mixture of acetone (15 ml) and water (0.5 ml), and thereto is added an acidic ion-exchange resin (IRA-20) (50 mg). The mixture is stirred at room temperature for two hours. After the reaction is complete, the acidic resin is removed by filtration, and the filtrate is concentrated under reduced pressure. The residue is dissolved in dioxane (12 ml), and thereto are added resorcinol (456 mg) and acetate buffer (pH 3.8, 12 ml). To the mixture is added dropwise and gradually aqueous solution of sodium chlorite (374 mg), and the mixture is stirred at room temperature overnight. After the reaction is complete, the pH value of the mixture is adjusted to pH 1 with conc. hydrochloric acid, and the mixture is extracted with chloroform. The chloroform layer is washed, dried, and concentrated under reduced pressure. The precipitated crystals are collected by filtration with diethyl ether to give 4,5-dimethoxy-2-(3,4,5-trimethoxybenzoyl)benzoic acid (810 mg) as listed in Table 51.

Reference Examples 15-26

The corresponding compounds are treated in the same manner as in Reference Example 14 to give the compounds as listed in Tables 51 and 52.

Reference Example 27

A solution of 2-bromo-4,5-dimethoxybenzaldehyde dimethyl acetal (14.8 g) in tetrahydrofuran (50 ml) is cooled to –70°C, and thereto is added dropwise a 1.6 M solution of n-butyl lithium in hexane (33.4 ml) under nitrogen atmosphere over a period of 20 minutes. The mixture is reacted at –60°C for 30 minutes, and thereto is added dropwise a solution of 2,3,4-trimethoxybenz-

aldehyde (10.0 g) in tetrahydrofuran (30 ml) over a period of 10 minutes. After reaction for one hour, to the mixture are added water and ethyl acetate (200 ml). The ethyl acetate layer is separated, washed, dried, and thereto is added an acidic ion-exchange resin (IRA-120) (7.0 g). The mixture is allowed to stand at room temperature for one hour. The mixture is filtered, and the filtrate is concentrated under reduced pressure. To the resultant are added pyridine (150 ml), 1.8M aqueous potassium hydroxide solution (150 ml), and the mixture is warmed to 80°C. To the mixture is added solid potassium permanganate (24.1 g) in portions, and the mixture is reacted at the same temperature for one hour. The insoluble materials are removed by filtration, and to the filtrate are added conc. hydrochloric acid (200 ml) and ethyl acetate (300 ml) under ice-cooling. The ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure. The residue is crystallized from diethyl ether to give 4,5-dimethoxy-6-(2,3,4-trimethoxybenzoyl)benzoic acid (7.72 g) as listed in Table 52.

Reference Example 28

The corresponding starting compounds are treated in the same manner as in Reference Example 27 to give 4,5-dimethoxy-2-(3,4-methylenedioxy-benzoyl)benzoic acid as listed in Table 52.

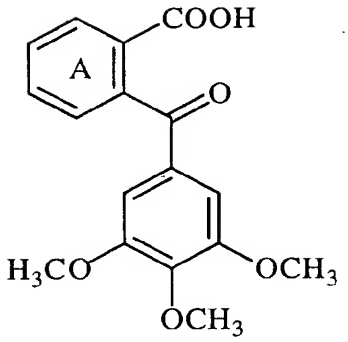
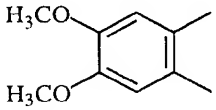
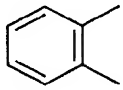
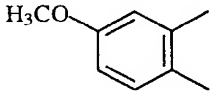
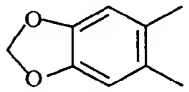
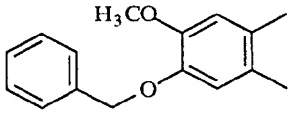
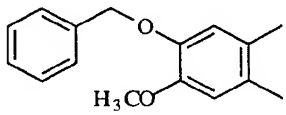
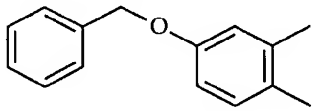
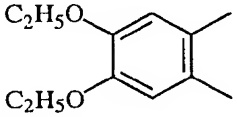


Table 51

Ref. Ex. No.	Ring A	Physicochemical properties
14		m.p. 182-184°C
15		m.p. 169-171°C
16		m.p. 197-199°C
17		m.p. 214-216°C
18		m.p. 146-147°C
19		m.p. 93-94°C
20		m.p. 161-162°C
21		m.p. 194-196°C

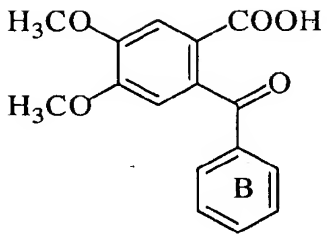
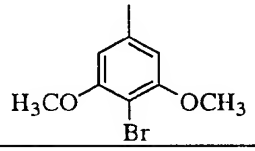
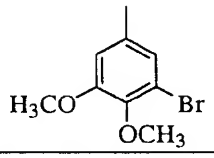
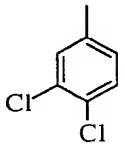
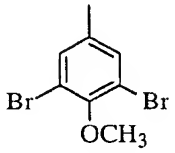
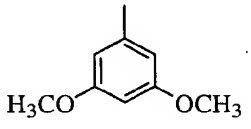
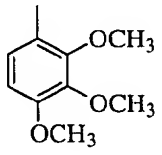
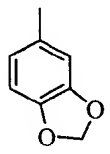


Table 52

Ref. Ex. No.	Ring A	Physicochemical properties
22		m.p. >230°C
23		m.p. 180-182°C
24		m.p. 189-191°C
25		m.p. 213-216°C
26		Oil
27		m.p. 166-168°C
28		m.p. 200-202°C

Reference Example 29

A solution of 2-(4-methoxyphenyl)-4,4-dimethyl-2-oxazoline (11.0 g) in tetrahydrofuran (50 ml) is cooled to –50°C, and thereto is added dropwise a 1.6 M solution of n-butyl lithium in hexane (36.8 ml) over a period of 20 minutes. The mixture is stirred at –40°C for 30 minutes, and thereto is added dropwise a solution of 3,4,5-trimethoxybenzaldehyde (10.5 g) in tetrahydrofuran (30 ml) at the same temperature over a period of 10 minutes. After reaction at –30°C for one hour, to the mixture are added water and ethyl acetate. The ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure. The residue is crystallized from diethyl ether to give 2-{2-[hydroxy-(3,4,5-trimethoxyphenyl)methyl]-4-methoxyphenyl}-4,4-dimethyl-2-oxazoline (16.2 g) as listed in Table 53.

Reference Example 30

The corresponding compounds are treated in the same manner as in Reference Example 29 to give 2-[2-hydroxy-(3,4,5-trimethoxyphenyl)methyl-phenyl]-4,4-dimethyl-2-oxazoline as listed in Table 53.

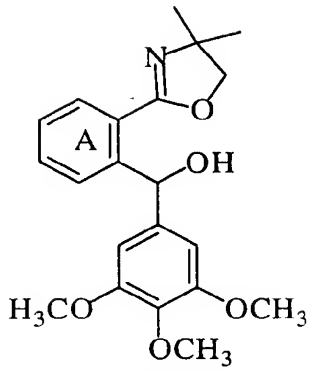
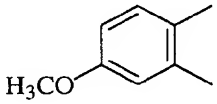
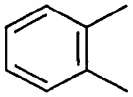


Table 53

Ref. Ex. No.	Ring A	Physicochemical properties
29		m.p. 109-110°C
30		Oil

Reference Example 31

A solution of N-methyl-2-chlorobenzamide (13.0 g) in tetrahydrofuran (300 ml) is cooled to –70°C, and thereto is added dropwise a 1.3M solution of sec-butyl lithium in cyclohexane (130 ml) over a period of 20 minutes. The mixture is stirred at –60°C for 30 minutes, and thereto is added dropwise a solution of 3,4,5-trimethoxybenzaldehyde (15.0 g) in tetrahydrofuran (100 ml) over a period of 10 minutes. The mixture is stirred at the same temperature for one hour, and thereto are added water and ethyl acetate (300 ml). The ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure. The residue is crystallized from diethyl ether to give N-methyl-2-chloro-6-[hydroxy-(3,4,5-trimethoxyphenyl)methyl]benzamide (19.2 g) as listed in Table 54.

Reference Example 32-35

The corresponding compounds are treated in the same manner as in Reference Example 31 to give the compounds as listed in Table 54.

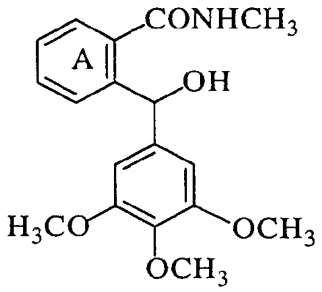
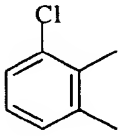
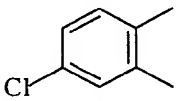
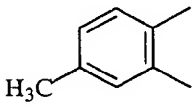
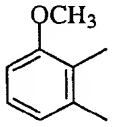
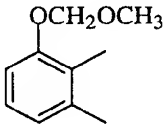


Table 54

Ref. Ex. No.	Ring A	Physicochemical properties
31		m.p. 185-187°C
32		Not purified
33		m.p. 138-140°C
34		m.p. 169-171°C
35		m.p. 148-149°C

Reference Example 36

To the compound obtained in Reference Example 29 (9.0 g) are added dioxane (38 ml) and conc. hydrochloric acid (19 ml). After reaction at 110°C for one hour, to the mixture are added water and ethyl acetate (150 ml). The ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure. The residue is crystallized from diethyl ether to give 5-methoxy-3-(3,4,5-trimethoxyphenyl)phthalide (6.14 g) as listed in Table 55.

Reference Example 37-41

The corresponding compounds are treated in the same manner as in Reference Example 36 to give the compounds as listed in Table 55.

Reference Example 42

To 6-[hydroxy-(3,4,5-trimethoxyphenyl)methyl]-2-methoxymethyloxy-N-methylbenzamide (the compound obtained in Reference Example 35) (17.0 g) are added dioxane (68 ml) and conc. hydrochloric acid (17 ml), and the mixture is stirred at 100°C for 20 minutes. To the mixture are added water and ethyl acetate (200 ml). The ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure. The residue is crystallized from diethyl ether. To the collected crystals are added dimethylformamide (90 ml), potassium carbonate (3.35 g), and benzyl bromide (4.14 g), and the mixture is stirred at room temperature for two hours. To the mixture are added water and ethyl acetate (200 ml). The ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure. The residue is crystallized from diethyl ether to give 7-benzyloxy-3-(3,4,5-trimethoxyphenyl)phthalide (7.68 g) as listed in Table 55.

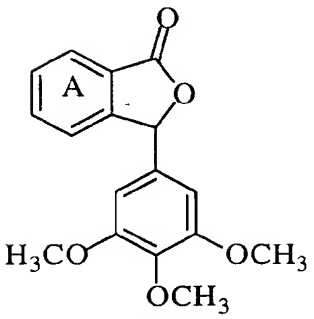
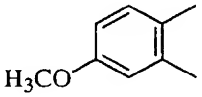
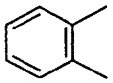
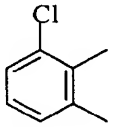
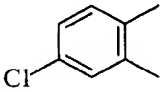
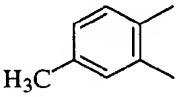
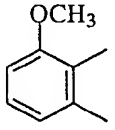
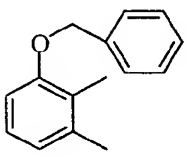


Table 55

Ref. Ex. No.	Ring A	Physicochemical properties
36		m.p. 114-115°C
37		m.p. 126-127°C
38		m.p. 199-201°C
39		m.p. 155-156°C
40		m.p. 107-110°C
41		m.p. 140-141°C
42		m.p. 148-149°C

Reference Example 43

To the compound obtained in Reference Example 36 are added pyridine (45 ml) and a 25 % aqueous potassium hydroxide solution (90 ml), and the mixture is warmed to 70°C. To the mixture is added solid potassium permanganate (5.31 g) in portions, and the mixture is stirred at the same temperature for 1.5 hour. The insoluble materials are removed by filtration, and to the filtrate are added conc. hydrochloric acid (100 ml) and ethyl acetate (300 ml) under ice-cooling. The ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure. The residue is crystallized from diethyl ether to give 4-methoxy-2-(3,4,5-trimethoxybenzoyl)benzoic acid (7.38 g) as listed in Table 56.

Reference Examples 44-49

The corresponding compounds are treated in the same manner as in Reference Example 43 to give the compounds as listed in Table 56.

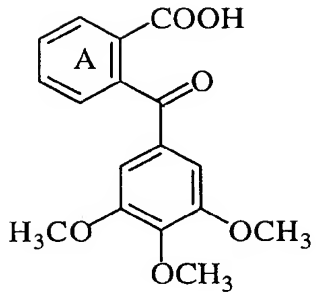
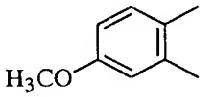
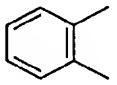
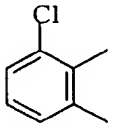
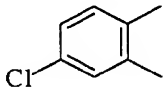
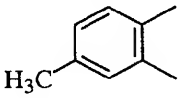
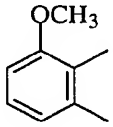
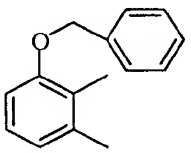


Table 56

Ref. Ex. No.	Ring A	Physicochemical properties
43		m.p. 207-209°C
44		m.p. 169-171°C
45		m.p. 169-171°C
46		m.p. 219-220°C
47		m.p. 182-183°C
48		m.p. 160-162°C
49		m.p. 153-155°C

Reference Example 50

To a solution of 4,5-dimethoxy-2-(3,4,5-trimethoxybenzoyl)benzoic acid (5 g) in dimethylformamide (50 ml) are added potassium carbonate (3.72 g) and diethyl bromomalonate (2.48 ml), and the mixture is stirred at room temperature overnight. The mixture is evaporated to remove dimethylformamide, and thereto is added chloroform and water. The chloroform layer is separated, and thereto are added dioxane (80 ml) and conc. hydrochloric acid (80 ml). The mixture is heated under reflux for three hours. The reaction mixture is cooled, and the precipitated crystals are collected by filtration washed with acetone, and dried to give 6,7-dimethoxy-4-(3,4,5-trimethoxyphenyl)isocoumarin-3-carboxylic acid (2.85 g) as listed in Table 57.

Reference Examples 51-59

The corresponding compounds are treated in the same manner as in Reference Example 50 to give the compounds as listed in Table 57.

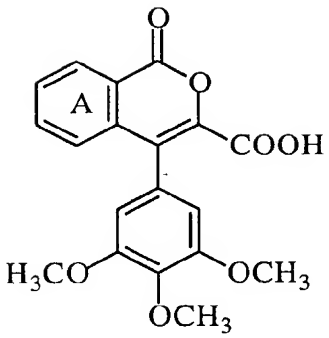
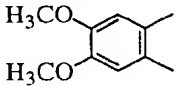
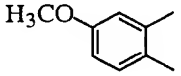
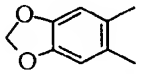
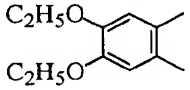
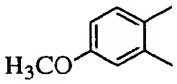
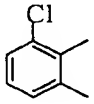
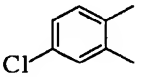
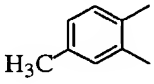
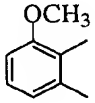


Table 57

Ref. Ex. No.	Ring A	Physicochemical properties
50		m.p. >250°C
51		m.p. 237-239°C
52		m.p. 264-266°C
53		m.p. 259-262°C
54		m.p. >250°C
55		m.p. 219-221°C
56		m.p. 234-236°C
57		m.p. >250°C
58		m.p. 233-235°C (decomp.)
59		m.p. 245-248°C

Reference Example 60

To a solution of 2-(3-bromo-4,5-dimethoxybenzoyl)-4,5-dimethoxybenzoic acid (6 g) in dimethylformamide (110 ml) are added potassium carbonate (4.29 g) and diethyl bromomalonate (3.71 g), and the mixture is stirred at room temperature overnight. The reaction mixture is evaporated to remove dimethylformamide, and to the residue are added ethyl acetate and water. The ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure. To the residue are added dioxane (35 ml) and conc. hydrochloric acid (35 ml), and the mixture is heated under reflux for five hours. The reaction mixture is cooled, and thereto are added chloroform and water. The chloroform layer is separated, washed, dried, and concentrated under reduced pressure. The residue is crystallized from ether to give 4-(3-bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-isocoumarin-3-carboxylic acid (2.54 g) as listed in Table 58.

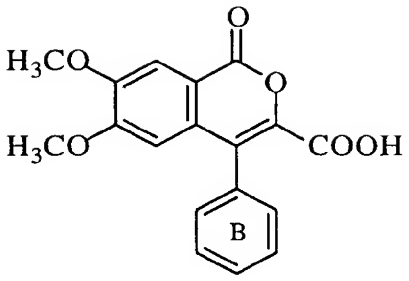
Reference Examples 61-65

The corresponding compounds are treated in the same manner as in Reference Example 60 to give the compounds as listed in Table 58.

Reference Example 66

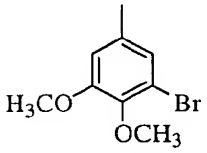
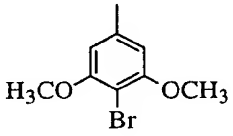
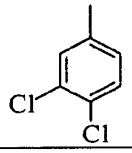
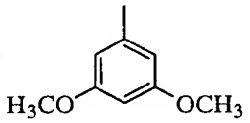
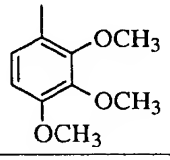
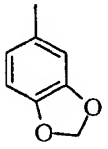
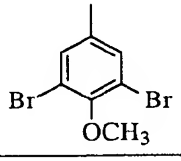
To a solution of 2-(3,5-dibromo-4-methoxybenzoyl)-4,5-dimethoxybenzoic acid (6.30 g) in dimethylformamide (50 ml) are added potassium carbonate (4.04 g) and dimethyl bromomalonate (3.43 g), and the mixture is stirred at room temperature overnight. To the reaction mixture are added ethyl acetate and water. The ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure. To the residue are added dioxane (30 ml) and conc. hydrochloric acid (30 ml), and the mixture is heated under reflux for five hours. The reaction mixture is cooled, and thereto are added ethyl acetate

and water. The ethyl acetate layer is separated, and washed. The remaining aqueous layer is acidified with 10 % hydrochloric acid, and then extracted with ethyl acetate. The extract is washed, and dried. The extracts are combined, and concentrated under reduced pressure. The residue is crystallized from ether to give 4-(3,5-dibromo-4-methoxyphenyl)-6,7-dimethoxy-isocoumarin-3-carboxylic acid (1.32 g) as listed in Table 58.



5

Table 58

Ref. Ex. No.	Ring B	Physicochemical properties
60		m.p. 260-262°C
61		Not purified
62		m.p. 274-277°C
63		m.p. 238-240°C
64		m.p. 215-218°C
65		m.p. 203-205°C
66		m.p. >250°C

Reference Example 67

To a solution of 5-benzyloxy-4-methoxy-2-(3,4,5-trimethoxybenzoyl)-benzoic acid (90 g) in dimethylformamide (900 ml) are added potassium carbonate (60.5 g) and di-tert-butyl bromomalonate (64.6 g), and the mixture is stirred at room temperature for three hours. To the reaction mixture are added ethyl acetate and water. The ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure. To the residue is added a 4M solution of hydrogen chloride in ethyl acetate (500 ml), and the mixture is stirred at room temperature for five hours. The precipitated crystals are collected by filtration, washed, dried, and dissolved in a mixture of acetic acid (40 ml) and dioxane (80 ml). The mixture is heated under reflux for five hours, and the precipitated crystals are collected by filtration, washed, and dried to give 7-benzyloxy-6-methoxy-4-(3,4,5-trimethoxyphenyl)isocoumarin-3-carboxylic acid (70.0 g) as listed in Table 59.

Reference Examples 68-70

The corresponding compounds are treated in the same manner as in Reference Example 67 to give the compounds as listed in Table 59.

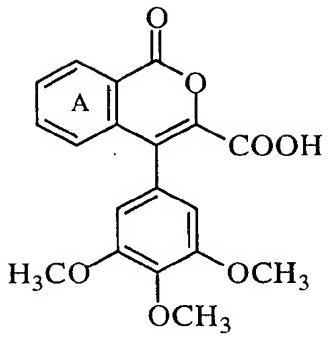
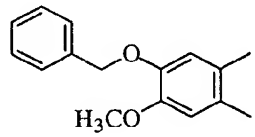
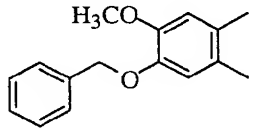
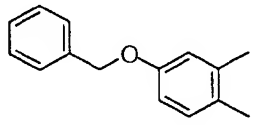
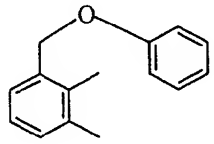


Table 59

Ref. Ex. No.	Ring A	Physicochemical properties
67		m.p. >250°C
68		m.p. 242-244°C
69		m.p. 236-238°C
70		m.p. 212-214°C

Reference Example 71

The compound obtained in Reference Example 67 (13.9 g) is added to a mixture of 2M aqueous sodium hydroxide solution (100 ml) and methanol (100 ml), and the mixture is stirred at room temperature for four hours. The mixture is concentrated under reduced pressure, and the remaining aqueous layer is adjusted to pH 2 with 10 % hydrochloric acid. The mixture is extracted with

ethyl acetate, and the extract is washed, dried, and concentrated under reduced pressure. The residue is crystallized from diethyl ether to give 7-benzyloxy-3-hydroxy-6-methoxy-4-(3,4,5-trimethoxyphenyl)-3,4-dihydroisocoumarin-3-carboxylic acid (12.78 g) as listed in Table 60.

Reference Examples 72-86

The corresponding compounds are treated in the same manner as in Reference Example 71 to give the compounds as listed in Table 60.

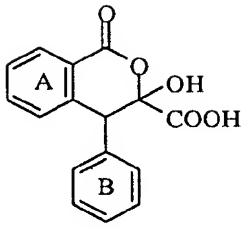


Table 60 (No. 1)

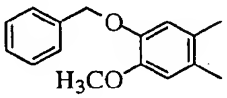
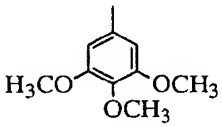
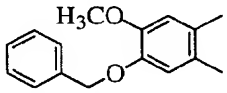
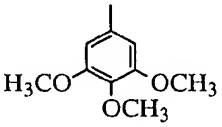
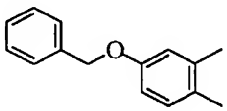
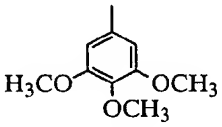
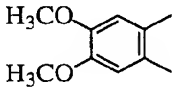
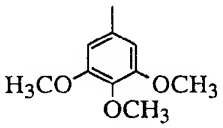
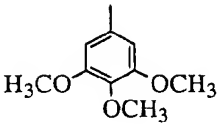
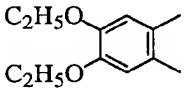
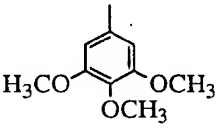
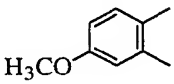
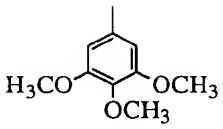
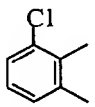
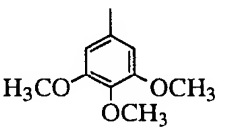
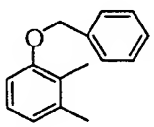
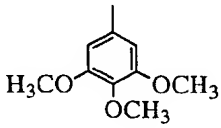
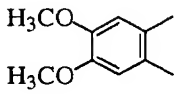
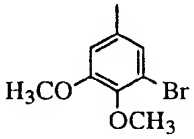
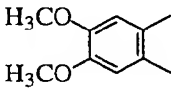
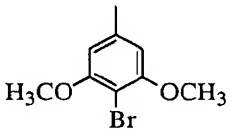
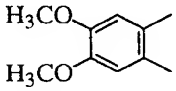
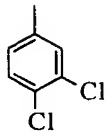
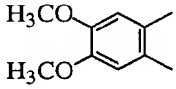
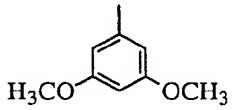
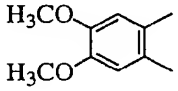
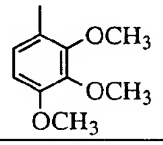
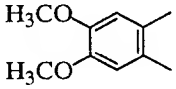
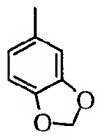
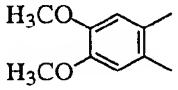
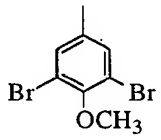
Ref. Ex. No.	Ring A	Ring B	Physicochemical properties
71			m.p. 160-163°C
72			m.p. 114-116°C
73			m.p. 105-106°C
74			m.p. 207-208°C
75			Powder
76			m.p. >250°C
77			Not purified
78			Not purified
79			m.p. 118-120°C

Table 60 (No. 2)

Ref. Ex. No.	Ring A	Ring B	Physicochemical properties
80			m.p. 258-260°C
81			Powder
82			Not purified
83			m.p. 165-168°C
84			Not purified
85			Not purified
86			Not purified

Reference Examples 87-91

5-Benzyloxy-2-bromo-4-methoxybenzaldehyde dimethyl acetal or 5-benzyloxy-2-bromobenzaldehyde dimethyl acetal is treated in the same manner as in Reference Example 1 or 9 to give the compounds as listed in Table 61.

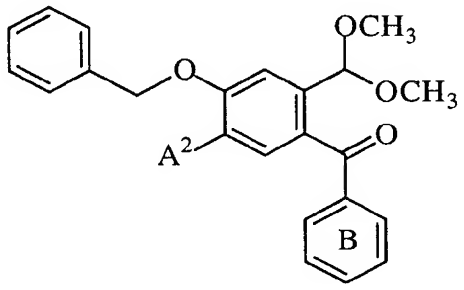
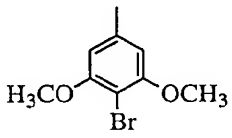
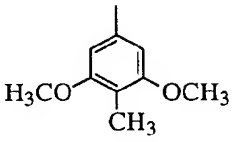
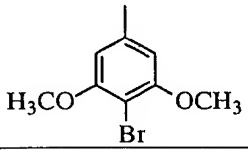
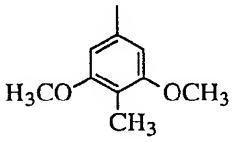
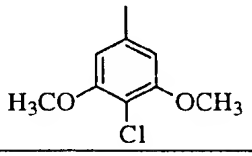


Table 61

Ref. Ex. No.	A^2	Ring B	Physicochemical properties
87	CH_3O–		not purified
88	CH_3O–		not purified
89	H		not purified
90	H		m.p. 134-136°C
91	H		m.p. 162-164°C

Reference Examples 92-96

The corresponding starting compounds (the compounds obtained in Reference Examples 87-91) are treated in the same manner as in Reference Example 14 to give the following compounds as listed in Table 62.

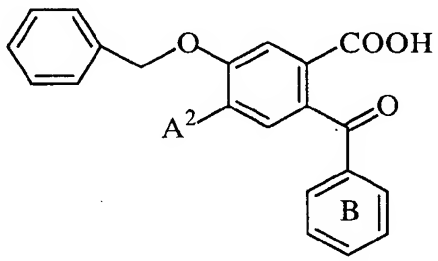
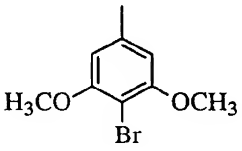
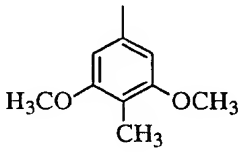
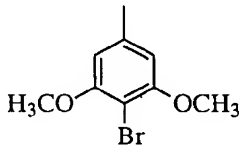
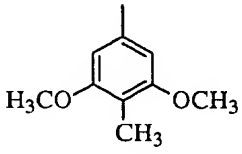
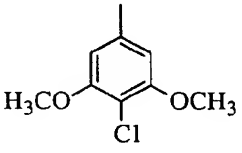


Table 62

Ref. Ex. No.	A^2	Ring B	Physicochemical properties
92	CH_3O–		m.p. 111-112°C
93	CH_3O–		m.p. 183-184°C
94	H		m.p. 179-180°C
95	H		m.p. 173-175°C
96	H		m.p. 173-175°C

Reference Examples 97-101

The corresponding starting compounds (the compounds obtained in Reference Examples 92-96) are treated in the same manner as in Reference Example 67 to give the following compounds as listed in Table 63.

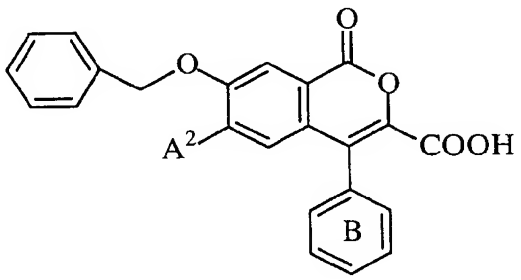
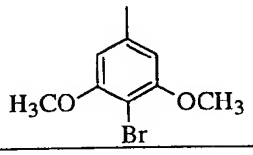
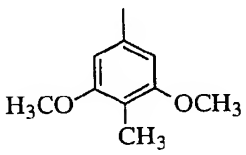
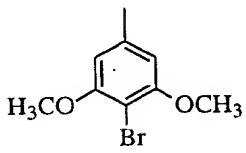
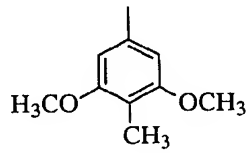
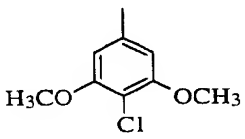


Table 63

Ref. Ex. No.	A^2	Ring B	Physicochemical properties
97	CH_3O–		m.p. >250°C
98	CH_3O–		m.p. >250°C
99	H		m.p. >250°C
100	H		m.p. 245-246°C
101	H		m.p. >250°C

Reference Examples 102-106

The corresponding starting compounds (the compounds obtained in Reference Examples 97-101) are treated in the same manner as in Reference Example 71 to give the following compounds as listed in Table 64.

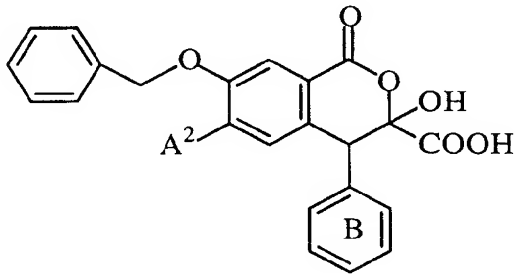
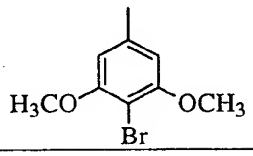
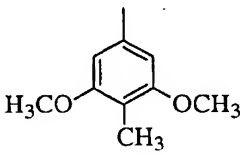
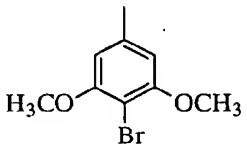
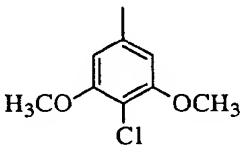
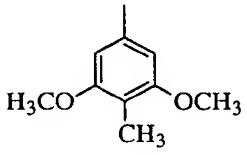


Table 64

Ref. Ex. No.	A^2	Ring B	Physicochemical properties
102	CH_3O–		m.p. 200-204°C (decomp.)
103	CH_3O–		m.p. 144-145°C (decomp.)
104	H		m.p. 113-115°C
105	H		m.p. 146-148°C
106	H		m.p. 129-134°C (decomp.)

Reference Example 107

(1) A solution of 2-bromo-5-benzyloxybenzaldehydedimethylacetal (8.14 g) in tetrahydrofuran (40 ml) is cooled at –78°C under nitrogen atmosphere, and a 1.6M n-butyl lithium (16.6 ml) is added thereto dropwise. The mixture is stirred for 10 minutes, and then a solution of N,N-dimethyl-3,4-dimethoxy-5-methoxymethoxybenzamide (6.50 g) in tetrahydrofuran is added thereto dropwise. After being warmed at ice-cooling temperature slowly, the mixture is poured into a saturated aqueous ammonium chloride solution, and extracted with ethyl acetate. The extract is washed, dried, and concentrated under reduced pressure to give a crude 2-(3,4-dimethoxy-5-methoxymethoxybenzoyl)-5-benzyloxybenzaldehydedimethylacetal.

(2) To a solution of the compound thus obtained in tetrahydrofuran (80 ml) is added a 2M aqueous hydrochloric acid solution (20 ml), and stirred at room temperature overnight. The solvent is evaporated, and to the residue are added water and ethyl acetate. The ethyl acetate layer is separated, washed, dried, and concentrated under reduced pressure to give 2-(3,4-dimethoxy-5-methoxymethoxybenzoyl)-5-benzyloxybenzaldehyde (5.66 g).

(3) The residual oil thus obtained is dissolved in dioxane (60 ml), and resorcinol (2.14 g) and acetate buffer (pH 3.8) (50 ml) are added thereto. To the mixture is added dropwise slowly an aqueous sodium chlorite solution, and the mixture is stirred at room temperature overnight. After the reaction, the reaction mixture is adjusted to pH 1 with conc. hydrochloric acid solution, and extracted with chloroform. The chloroform layer is washed, dried, and concentrated under reduced pressure to give 2-(3,4-dimethoxy-5-methoxymethoxybenzoyl)-5-benzyloxybenzoic acid.

(4) The compound thus obtained is dissolved in dimethylformamide (30 ml). Potassium carbonate (1.79 g) and di-tert-butyl bromomalonate (3.83 g) are added thereto under ice-cooling, and the mixture is stirred at room temperature overnight. Then potassium carbonate (1.79 g) is added thereto. After being stirred overnight, the mixture is poured into water. The mixture is extracted with ethyl acetate, and the extract is washed, dried, and concentrated under reduced pressure. To the residue is added a 4M solution of hydrogen chloride in ethyl acetate (35 ml), and the mixture is stirred overnight. The mixture is concentrated under reduced pressure and then co-evaporated with dioxane. The residue is dissolved in dioxane (50 ml) and acetic acid (30 ml), and the mixture is heated under reflux for 4 hours. The mixture is concentrated under reduced pressure and co-evaporated with toluene. The residue is dissolved in dimethylformamide (50 ml), and to the mixture diisopropylethylamine (9.3 ml) and methoxymethyl chloride (4.0 ml) are added under ice-cooling temperature. The mixture is stirred overnight, and poured into water. The mixture is extracted with ethyl acetate, and the extract is washed, dried, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; hexane:chloroform:ethyl acetate = 5:5:1) to give 7-benzyloxy-4-(3,4-dimethoxy-5-methoxymethoxyphenyl)-3-methoxymethoxycarbonyloxy-isocoumarin (1.82 g).

(5) The compound thus obtained is dissolved in tetrahydrofuran (15 ml) and methanol (5 ml), and to the solution a 2M aqueous sodium hydroxide solution (3.39 ml) is added. The mixture is stirred for 20 minutes, and then a 2M aqueous hydrochloric acid solution is added thereto. The mixture is concentrated under reduced pressure, and water and ethyl acetate are added thereto. The ethyl

acetate layer is washed, dried, and concentrated under reduced pressure to give 7-benzyloxy-3-hydroxy-4-(3,4-dimethoxy-5-methoxymethoxyphenyl)-3,4-dihydroisocoumarin-3-carboxylic acid.

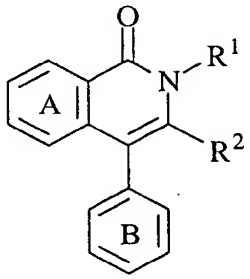
INDUSTRIAL APPLICABILITY

The present compound (I) and a pharmaceutically acceptable salt thereof show a cGMP-specific PDE inhibitory activity, especially, selective phosphodiesterase V (PDE V) inhibitory activity. The compound (I) show excellent vasodilating activity, activity of reducing pulmonary arterial pressure, activity of increasing intracavernous pressure, relaxation activity of isolated blood vessel, inhibitory activity of vascular smooth muscle growth, inhibitory activity of cardiac hypertrophy, inhibitory activity of platelet aggregation, and the like. Therefore, the compounds of the present invention are useful, for example, as a medicament in the prophylaxis or treatment of chronic heart failure, angina, penile erectile dysfunction (copulative impotence), female sexual dysfunction, hypertension, pulmonary hypertension, arteriosclerosis, or in the prophylaxis or treatment of restenosis after percutaneous transluminal coronary angioplasty (PTCA).

Besides, the present compound (I) or a pharmaceutically acceptable salt thereof hardly show any side effects and has low toxicity. Therefore, they show a high safety as a medicament.

CLAIMS

1. An isoquinolinone derivative of the formula (I):



(I)

wherein Ring A and Ring B are the same or different and each a substituted or unsubstituted benzene ring, R^1 is (1) a hydrogen atom, (2) a substituted or unsubstituted lower alkyl group, (3) a substituted or unsubstituted cyclo-lower alkyl group, (4) a substituted or unsubstituted aryl group, (5) a substituted or unsubstituted heterocyclic group, or (6) an amino group optionally having one or two substituents, R^2 is a group of the formula $-COOR^3$ or $-CON(R^4)(R^5)$, R^3 is a hydrogen atom or an ester residue, and a group of the formula $-N(R^4)(R^5)$ is a substituted or unsubstituted nitrogen-containing aliphatic heterocyclic group or a substituted or unsubstituted amino group, provided that when R^1 is a hydrogen atom or a substituted or unsubstituted lower alkyl group, then at least one of Ring A and Ring B is a benzene ring being substituted by two or more lower alkoxy groups, or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein the ester residue for R^3 is a lower alkyl group, a tri-lower alkylsilyl-lower alkyl group, or an aryl-lower alkyl group, and a group of the formula $-N(R^4)(R^5)$ is a hydroxy-lower alkyl-substituted piperazinyl group, a morpholino group, a pyrrolidinyl group,

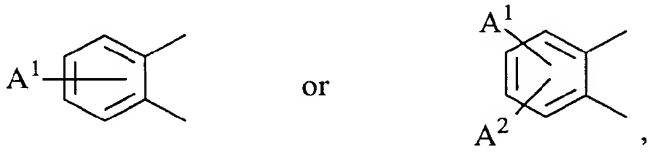
an imidazolyl-substituted lower alkylamino group, or a mono- or di-lower alkylamino group.

3. The compound according to claim 1, wherein Ring A and Ring B are a benzene ring which may optionally have 1 to 4 substituents being the same or different, and said substituents of Ring A and Ring B are a member selected from a protected or unprotected hydroxy group, a lower alkylenedioxy group, a halogen atom, a lower alkyl group, a mono- or di-lower alkylcarbamoyloxy group, and a group of the formula R^6–$(CO)_n$–O– (R^6 is a substituted or unsubstituted lower alkyl group, a substituted or unsubstituted lower alkenyl group, a substituted or unsubstituted cyclo-lower alkyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted arylsulfonyl group, or a substituted or unsubstituted heterocyclic group, and n is 0 or 1).

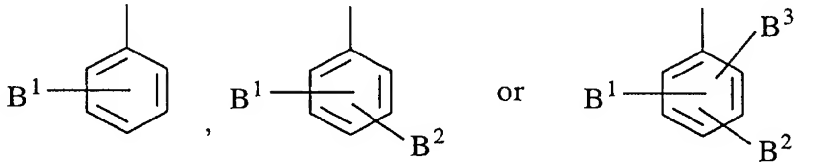
4. The compound according to claim 1, wherein Ring A is a benzene ring which may optionally have 1 to 4 substituents being the same or different, and said substituents of Ring A are a member selected from a protected or unprotected hydroxy group, a lower alkylenedioxy group, a halogen atom, a lower alkyl group, a mono- or di-lower alkylcarbamoyloxy group, and a group of the formula R^6–$(CO)_n$–O– (R^6 is a substituted or unsubstituted lower alkyl group, a substituted or unsubstituted lower alkenyl group, a substituted or unsubstituted cyclo-lower alkyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted arylsulfonyl group, or a substituted or unsubstituted heterocyclic group, and n is 0 or 1), Ring B is a benzene ring which may optionally have 1 to 4 substituents being the same or different, and said substituents of Ring B is a member selected from a protected or

unprotected hydroxy group, a lower alkoxy group, a lower alkyl group, a halogen atom, and a lower alkylenedioxy group.

5. The compound according to claim 4, wherein Ring A is a benzene ring of the formula:



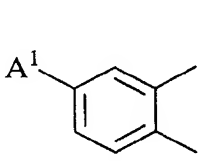
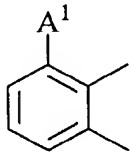
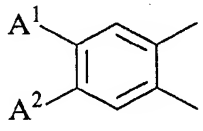
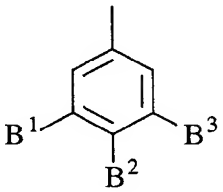
Ring B is a benzene ring of the formula:



A^1 and A^2 are the same or different and each a member selected from a hydrogen atom, a protected or unprotected hydroxy group, a lower alkylenedioxy group, a halogen atom, a lower alkyl group, a mono- or di-lower alkylcarbamoyloxy group, and a group of the formula R^6–$(CO)_n$–O– (R^6 and n are the same as defined above), B^1, B^2 and B^3 are the same or different and each a member selected from a protected or unprotected hydroxy group, a lower alkoxy group, a lower alkyl group, a halogen atom and a lower alkylenedioxy group.

6. The compound according to claim 5, wherein R^6 is (1) a lower alkyl group which may optionally be substituted by a group selected from a 5- to 10-membered heteromonocyclic or heterobicyclic group being optionally substituted by a hydroxy-substituted lower alkyl group, a lower alkyl group, an

oxo group or a lower alkoxycarbonyl group; a 6- to 10-membered heteromonocyclic or heterobicyclic aryl group being optionally substituted by a lower alkylenedioxy group, a carboxyl group, a lower alkoxycarbonyl group, a lower alkoxy group, a sulfamoyl group, a carbamoyl group, a nitro group, a protected or unprotected amino group, a phenyl group, a halogen atom, a mono-lower alkylamino group, a di-lower alkylamino group, a lower alkylpiperazinocarbonyl group, a hydroxy-substituted lower alkyl group or a lower alkyl group; a cyano group; a carboxyl group; a mono- or di-lower alkylamino group; a lower alkoxy-substituted lower alkoxy group; a lower alkoxy group; a hydroxy group; a carbamoyl group; a lower alkoxycarbonyl group; a cyclo-lower alkyl group; and a benzoyl group, or (2) a 5- to 10-membered heteromonocyclic or heterobicyclic group which may optionally be substituted by a group selected from a lower alkyl group, a cyano group, a carboxyl group, a mono- or di-lower alkylamino group, a lower alkoxy-substituted lower alkyl group, a hydroxy group, a lower alkoxy group, a carbamoyl group, a lower alkoxycarbonyl group and a nitro group.

7. The compound according to claim 5, wherein Ring A is a benzene ring of the formula:  ,  or  , and Ring B is a benzene ring of the formula:  , wherein A^1, A^2, B^1, B^2 and B^3 are the same as defined in claim 5.

8. The compound according to any one of claim 5, 6, or 7, wherein A^1 and A^2 are the same or different and each a protected or unprotected hydroxy group; a lower alkoxy group which may optionally be substituted by a group selected from a lower alkylenedioxyphenyl group, a benzimidazolyl group, a lower alkyl-substituted imidazolyl group, a cyano group, a carboxyl group, a pyridyl group, an N-oxopyridyl group, a pyridyl group being substituted by a hydroxy-substituted lower alkyl group, a pyrrolidinyl group, an isoquinolyl group, a pyrimidinyl group, a pyrazinyl group, a quinazolyl group, a phthalazinyl group, a lower alkoxycarbonyl-substituted piperidinyl group, a piperidyl group, a quinolyl group, a tetrazolyl group, a thienyl group, a furyl group, a pyrrolyl group being substituted by a lower alkyl group and a lower alkoxycarbonyl group, a mono- or di-lower alkyl amino group, a lower alkoxy-substituted lower alkoxy group, a lower alkoxy group, a hydroxy group, a carbamoyl group, a lower alkoxycarbonyl group, a cyclo-lower alkyl group, a carboxy-substituted phenyl group, a lower alkoxycarbonyl group-substituted phenyl group, a benzoyl group, a mono- or di-lower alkoxy-substituted phenyl group, a nitro-substituted phenyl group, a naphthyl group, a mono- or di-halogenophenyl group, a carbamoyl-substituted phenyl group, a sulfamoyl-substituted phenyl group, a phenyl group being substituted by one or two protected or unprotected amino groups, a biphenyl group, a phenyl group being substituted by a halogen atom and a nitro group, a mono-lower alkylamino-substituted phenyl group, a di-lower alkylamino-substituted phenyl group, a lower alkylpiperazinocarbonyl-substituted phenyl group, and a lower alkyl-substituted phenyl group; a lower alkylenedioxy group; a halogen atom; a lower alkyl group; a cyclo-lower alkoxy group; a pyridyloxy group; a lower

alkenyloxy group; a morpholinocarbonyloxy group; a lower alkyl-substituted piperazinylcarbonyloxy group; a pyrrolylcarbonyloxy group being substituted by a lower alkyl group and a nitro group; a pyrrolylcarbonyloxy group; a mono- or di-lower alkylcarbamoyloxy group; a lower alkyl-substituted phenylsulfonyloxy group; or a benzoyloxy group.

9. The compound according to claim 8, wherein R^1 is (1) a hydrogen atom, (2) a lower alkyl group being optionally substituted by a group selected from a piperidinyl group, a pyridyl group, an imidazolyl group, a lower alkyl-substituted piperidyl group, a furyl group, a morpholino group, a tetrahydrofuryl group, a dihydropyridyl group being substituted by a lower alkyl group and an oxo group, a piperazinyl group, a lower alkoxycarbonyl-substituted piperazinyl group, a cyclo-lower alkyl group, a phenyl group, a lower alkylenedioxyphenyl group, a lower alkoxycarbonyl group, a hydroxy group, a hydroxy-substituted lower alkoxy group, a carboxyl group, a lower alkoxy group, a protected or unprotected amino group, a carbamoyl group, a di-lower alkylamino group, and a pyridylcarbonyloxy group, (3) a cyclo-lower alkyl group which may optionally be substituted by a lower alkoxycarbonyl group, a hydroxy group, a carboxyl group, or a protected or unprotected amino group, (4) a 6- to 14-membered monocyclic, bicyclic or tricyclic aryl group optionally being partially saturated, which may optionally be substituted by a group selected from a halogen atom, a mono- or di-lower alkylamino group, a morpholino group, a lower alkyl-substituted pyrimidinyl group, a lower alkyl-substituted pyrazolyl group, a hydroxy-substituted lower alkyl group, a protected or unprotected amino group, a lower alkanoyl-substituted amino group, a lower alkoxy group, a lower alkyl group, a protected or unprotected hydroxy group, a carboxy-

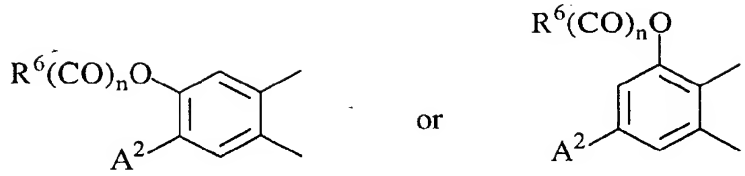
substituted lower alkyl group, a lower alkoxycarbonyl-substituted lower alkyl group, a lower alkoxycarbonyl-substituted lower alkoxy group, a carbamoyl group, a carboxyl group, a lower alkylthio group, a lower alkoxycarbonyl group, a nitro group, a tri-halogeno-lower alkyl group, a morpholinocarbonyl group, a carboxyl-substituted lower alkoxy group, a di-(lower alkylsulfonyl)-amino group, a morpholino-lower alkylcarbamoyl-substituted lower alkoxy group, a sulfamoyl group, a lower alkyl group being substituted by a protected or unprotected amino group, an amino group being substituted by a lower alkyl group and a protecting group for amino group, a lower alkylenedioxy group, a carbamoyl group being substituted a protected or unprotected amino group, a lower alkylsulfinyl group, and a lower alkylsulfonyl group, (5) a 5- to 12-membered heteromonocyclic or heterobicyclic group optionally being partially saturated, which may optionally be substituted by a group selected from a lower alkyl group, a phenyl-substituted lower alkyl group, a hydroxy-substituted lower alkyl group, an oxo group, a lower alkoxy group, a protected or unprotected amino group, a phenyl-lower alkoxycarbonyl group and a lower alkoxycarbonyl group, or (6) an amino group which may optionally be substituted by one or two groups selected from a protecting group for amino group, a pyridyl group, a lower alkanoyl group, a lower alkyl group, a hydroxy-substituted lower alkyl group, a phenyl group, a lower alkanoyloxy-substituted lower alkyl group, and a tri-halogeno-lower alkanoyl group.

10. The compound according to claim 9, wherein the 6- to 14-membered monocyclic, bicyclic or tricyclic aryl group is a phenyl group, an indanyl group, a fluorenyl group, or a naphthyl group, the 5- to 12-membered heteromonocyclic or heterobicyclic group is a piperazinyl group, a pyranyl

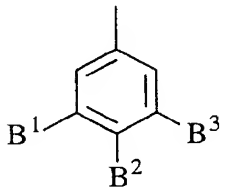
group, a morpholino group, an indazolyl group, a pyrrolidinyl group, an indolyl group, a benzotriazolyl group, a pyrazinyl group, a pyridyl group, a thiomorpholino group, a pyrrolyl group, a quinolyl group, an isoquinolyl group, a phthlazinyl group, an isooxazolyl group, or a piperidyl group,

11. The compound according to claim 7, wherein A^1 and A^2 are the same or different, and each a protected hydroxy group; a lower alkoxy group; a pyridyl-lower alkoxy group; a hydroxy-lower alkyl group-substituted pyridyl-lower alkoxy group; an N-oxopyridyl-lower alkoxy group; a pyrazinyl-lower alkoxy group; a quinolyl-lower alkoxy group; a lower alkoxy group being substituted by an amino-substituted phenyl group; a lower alkoxy group being substituted by a mono- or di-lower alkylamino-substituted phenyl group; a lower alkoxy group being substituted by a lower alkoxy-substituted phenyl group; a lower alkoxy group being substituted by a hydroxy-lower alkyl group-substituted phenyl group; a lower alkoxy group being substituted by a carboxy-substituted phenyl group; or an isoquinolyl-lower alkoxy group, B^1, B^2 and B^3 are the same or different, or each a halogen atom, a lower alkyl group, or a lower alkoxy group, R^1 is a phenyl group optionally being substituted by a protected or unprotected amino group, a pyridyl group optionally being substituted by a protected or unprotected amino group, or a morpholino group, and R^2 is a lower alkoxycarbonyl group or a phenyl-lower alkoxycarbonyl group.

12. The compound according to claim 5, wherein Ring A is a benzene ring of the formula:



and Ring B is a benzene ring of the formula:

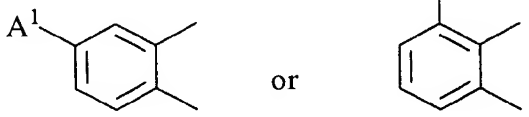


wherein A^2, B^1, B^2, B^3, R^6 and n are the same as defined in claim 5.

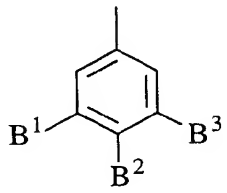
13. The compound according to claim 12, wherein R^6 is (1) a lower alkyl group which may optionally be substituted by a group selected from a pyrrolyl group optionally being substituted by a lower alkyl group or a lower alkoxycarbonyl group; a pyridyl group optionally being substituted by a hydroxy-substituted lower alkyl group; an N-oxopyridyl group; a pyrazinyl group; a thienyl group; a phenyl group optionally being substituted by 1 to 3 groups being the same or different, and selected from a carboxyl group, a lower alkoxycarbonyl group, a nitro group, an amino group, a mono- or di-lower alkyl-amino group, a phenyl group, a halogen atom, a lower alkoxy group, a hydroxy-substituted lower alkyl group and a lower alkyl group; a naphthyl group; a quinolyl group; an isoquinolyl group; a benzimidazolyl group; and a cyclo-lower alkyl group, or (2) a pyrrolyl group optionally being substituted by a group selected from a lower alkyl group and a nitro group, A^2 is a hydrogen atom or a lower alkoxy group, R^1 is a phenyl group, a phenyl group being substituted by a protected or unprotected amino group, or a morpholino group,

B^1, B^2 and B^3 are the same or different and each a halogen atom, a lower alkyl group, or a lower alkoxy group, and n is 0 or 1.

14. The compound according to claim 5, wherein Ring A is a benzene ring of the formula:



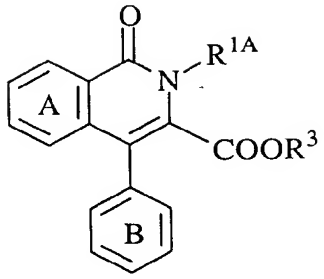
and Ring B is a benzene ring of the formula:



wherein A^1 is a protected or unprotected hydroxy group, or a lower alkoxy group being substituted by a group selected from a pyridyl group, an N-oxo-pyridyl group, a hydroxy-lower alkyl group-substituted pyridyl group, a pyrazinyl group, an amino group-substituted phenyl group, a mono- or di-lower alkylamino-substituted phenyl group, a lower alkoxy-substituted phenyl group, a hydroxy-lower alkyl group-substituted phenyl group, an isoquinolyl group, and a quinolyl group, B^1, B^2 and B^3 are the same or different and each a halogen atom, a lower alkyl group, or a lower alkoxy group, and R^1 is a phenyl group being optionally substituted by a protected or unprotected amino group.

15. The compound according to claim 13 or 14, wherein R^2 is a lower alkoxycarbonyl group.

16. An isoquinolinone derivative of the formula (I-A):



(I-A)

wherein Ring A and Ring B are the same or different and each a substituted or unsubstituted benzene ring, R^{1A} is a substituted or unsubstituted aryl group or a substituted or unsubstituted heterocyclic group, and R^3 is a hydrogen atom or an ester residue, or a pharmaceutically acceptable salt thereof.

17. The compound according to claim 16, wherein Ring A and Ring B are the same or different and each a benzene ring having optionally 1 to 4 substituents selected from

(i) a hydroxy group;

(ii) a halogen atom;

(iii) a lower alkyl group;

(iv) a cyclo-lower alkoxy group;

(v) a lower alkylenedioxy group;

(vi) a lower alkoxy group;

(vii) a lower alkoxy group having 1 to 3 substituents selected from a hydroxy group, a benzoyl group, a lower alkoxycarbonyl group, a carboxyl group, a mono- or di-lower alkylamino group, a lower alkoxy-lower alkoxy group, a lower alkoxy group, a phenyl group, a naphthyl group and a phenyl group having 1 to 3 substituents selected from a nitro group, a halogen atom, a phenyl group, a carboxyl group, a lower alkoxycarbonyl group, a lower alkyl

group, a lower alkoxy group, an amino group, a mono- or di-lower alkylamino group and a hydroxy-lower alkyl group; and

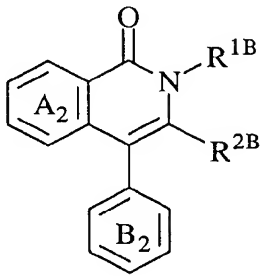
(viii) a lower alkoxy group being substituted by a 5- to 10-membered heterocyclic group having 1 to 4 heteroatoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, and optionally 1 to 3 substituents selected from a carboxyl group, a lower alkoxycarbonyl group, a lower alkyl group, a hydroxy-substituted lower alkyl group, a nitro group and an oxo group,

R^{1A} is a phenyl group; a phenyl group having 1 to 4 substituents selected from a protected or unprotected amino group, a halogen atom, a mono- or di-lower alkylamino group, a morpholino group, a lower alkyl-substituted pyrimidinyl group, a lower alkyl-substituted pyrazolyl group, a hydroxy-substituted lower alkyl group, a lower alkanoyl-substituted amino group, a lower alkoxy group, a lower alkyl group, a protected or unprotected hydroxy group, a carboxyl-substituted lower alkyl group, a lower alkoxycarbonyl-substituted lower alkyl group, a lower alkoxycarbonyl-substituted lower alkoxy group, a carbamoyl group, a carboxyl group, a lower alkylthio group, a lower alkoxycarbonyl group, a nitro group, a trihalogeno-lower alkyl group, a morpholinocarbonyl group, a carboxyl-substituted lower alkoxy group, a di-lower alkylsulfonyl-substituted amino group, a morpholino-lower alkylcarbamoyl-substituted lower alkoxy group, an amino group being substituted by a lower alkyl group and a protecting group for amino group, a lower alkylenedioxy group, a carbamoyl group being substituted by a protected or unprotected amino group, a lower alkylsulfinyl group and a lower alkylsulfonyl group; or a 5- to 10-membered heterocyclic group having 1 to 4 heteroatoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, said heterocyclic group

having 1 to 4 substituents selected from a hydroxy group, a halogen atom, a lower alkyl group, a phenyl-substituted lower alkyl group, a hydroxy-substituted lower alkyl group, an oxo group, a lower alkoxy group, a protected or unprotected amino group, a mono- or di-lower alkylamino group, a phenyl-substituted lower alkoxycarbonyl group, a lower alkoxycarbonyl group, a carboxyl group and a carbamoyl group, and

R^3 is a hydrogen atom or a lower alkyl group.

18. An isoquinolinone derivative of the formula (I-B):



(I-B)

wherein Ring A_2 and Ring B_2 are the same or different and each a benzene ring which may optionally be substituted by 1 to 4 groups selected from the group consisting of a protected or unprotected hydroxyl group; a lower alkylenedioxy group; a halogen atom; a lower alkyl group; a mono- or di-lower alkylcarbamoyl-oxy group; and a group of the formula: R^{6B}–$(CO)_n$–O

in which R^{6B} is

(i) a lower alkyl group which may optionally have 1 or 2 substituents selected from the group consisting of a 5- to 12-membered heteromonocyclic or heterobicyclic group having optionally 1 to 4 substituents selected from the group consisting of a hydroxy-substituted lower alkyl group, a lower alkyl group, an oxo group and a lower alkoxycarbonyl group; a phenyl or naphthyl

group having optionally 1 to 4 substituents selected from the group consisting of a protected or unprotected amino group, a lower alkylenedioxy group, a carboxyl group, a lower alkoxycarbonyl group, a lower alkoxy group, a sulfamoyl group, a carbamoyl group, a nitro group, a phenyl group, a halogen atom, a mono-lower alkylamino group, a di-lower alkylamino group, a lower alkylpiperazinocarbonyl group, a hydroxy-substituted lower alkyl group and a lower alkyl group; a cyano group; a carboxyl group; a mono- or di-lower alkylamino group; a lower alkoxy-substituted lower alkoxy group; a lower alkoxy group; a hydroxy group; a carbamoyl group; a lower alkoxycarbonyl group; a cyclo-lower alkyl group; and a benzoyl group,

(ii) a 5- to 12-membered heteromonocyclic or heterobicyclic group having optionally 1 to 4 substituents selected from the group consisting of a lower alkyl group, a cyano group, a carboxyl group, a mono- or di-lower alkylamino group, a lower alkoxy-substituted lower alkyl group, a hydroxy group, a lower alkoxy group, a carbamoyl group, a lower alkoxycarbonyl group and a nitro group,

(iii) a cyclo-lower alkyl group,

(iv) a lower alkenyl group, or

(v) a lower alkyl-substituted or unsubstituted phenylsulfonyl group,

n is an integer of 0 or 1,

R^{1B} is

(i) a hydrogen atom,

(ii) a lower alkyl group having optionally 1 to 3 substituents selected from the group consisting of a piperidyl group, a pyridyl group, an imidazolyl group, a lower alkyl-substituted piperidyl group, a furyl group, a morpholino

group, a tetrahydrofuryl group, a dihydropyridyl group being substituted by a lower alkyl group and an oxo group, a piperazinyl group, a lower alkoxy-carbonyl substituted-piperazinyl group, a cyclo-lower alkyl group, a phenyl group, a lower alkylenedioxy-phenyl group, a lower alkoxycarbonyl group, a hydroxyl group, a hydroxy-substituted lower alkoxy group, a carboxyl group, a lower alkoxy group, a protected or unprotected amino group, a carbamoyl group, a di-lower alkylamino group and a pyridylcarbonyloxy group,

(iii) a cyclo-lower alkyl group having optionally 1 to 3 substituents selected from the group consisting of a lower alkoxycarbonyl group, a hydroxy group, a carboxyl group, a lower alkyl group, a lower alkoxy group, a hydroxy-substituted lower alkoxy group and a protected or unprotected amino group,

(iv) an unsaturated or partially saturated 6- to 14-membered monocyclic, bicyclic or tricyclic aryl group having optionally 1 to 4 substituents selected from the group consisting of a halogen atom, a mono- or di-lower alkylamino group, a morpholino group, a lower alkyl-substituted pyrimidinyl group, a lower alkyl-substituted pyrazolyl group, a hydroxy-substituted lower alkyl group, a protected or unprotected amino group, a lower alkanoyl-substituted amino group, a lower alkoxy group, a lower alkyl group, a protected or unprotected hydroxy group, a carboxy-substituted lower alkyl group, a lower alkoxy-carbonyl-substituted lower alkyl group, a lower alkoxycarbonyl-substituted lower alkoxy group, a carbamoyl group, a carboxyl group, a lower alkylthio group, a lower alkoxycarbonyl group, a nitro group, a trihalogeno-lower alkyl group, a morpholinocarbonyl group, a carboxy-substituted lower alkoxy group, a di-lower alkylsulfonylamino group, a morpholino-lower alkyl carbamoyl-substituted lower alkyl group, a sulfamoyl group, a carbamoyl group being

optionally substituted by a protected or unprotected amino group, a lower alkylsulfinyl group and a lower alkylsulfonyl group,

(v) a 5- to 12-membered aromatic or aliphatic heteromonocyclic or heterobicyclic group having 1 to 4 substituents selected from the group consisting of a hydroxy group, a halogen atom, a phenyl-substituted lower alkyl group, a hydroxy-substituted lower alkyl group, an oxo group, a lower alkoxy group, a protected or unprotected amino group, a mono- or di-lower alkylamino group, a phenyl-lower alkoxycarbonyl group, a lower alkoxycarbonyl group, a carboxyl group and a carbamoyl group, or

(vi) an amino group having optionally 1 or 2 substituents selected from the group consisting of a protecting group for amino group, a pyridyl group, a lower alkanoyl group, a lower alkoxy group, a hydroxy-substituted lower alkyl group, a phenyl group, a lower alkanoyloxy-substituted lower alkyl group and a trihalogeno-lower alkanoyl group,

R^{2B} is a group of the formula: -$COOR^{3B}$ or a group of the formula:

–$CON(R^{4B})(R^{5B})$

R^{3B} is a hydrogen atom, a lower alkyl group, a tri-lower alkylsilyl group or a phenyl-lower alkyl group, and

a group of the formula:–$N(R^{4B})(R^{5B})$ is a hydroxy-lower alkyl-substituted piperazinyl group, a morpholino group, a pyrrolidinyl group, an imidazolyl-substituted lower alkylamino group or a mono- or di-lower alkylamino group, provided that when R^{1B} is one of the groups of the above-mentioned (i) or (ii), then at least one of Ring A_2 and Ring B_2 is a benzene ring which is substituted by two or more lower alkoxy groups,

or a pharmaceutically acceptable salt thereof.

19. 6-Methoxy-3-methoxycarbonyl-2-morpholino-7-(4-pyridylmethyl-oxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

6-methoxy-3-methoxycarbonyl-2-morpholino-7-(3-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

6-methoxy-3-methoxycarbonyl-2-morpholino-7-(2-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

6-methoxy-3-methoxycarbonyl-2-phenyl-4-(3,4,5-trimethoxyphenyl)-7-(4-pyridylmethyloxy)-1(2H)-isoquinolinone;

6-methoxy-3-methoxycarbonyl-2-phenyl-4-(3,4,5-trimethoxyphenyl)-7-(3-pyridylmethyloxy)-1(2H)-isoquinolinone;

6-methoxy-3-methoxycarbonyl-2-phenyl-4-(3,4,5-trimethoxyphenyl)-7-(2-pyridylmethyloxy)-1(2H)-isoquinolinone;

or a pharmaceutically acceptable salt thereof.

20. 2-(4-Aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(2-pyridyl-methyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(3-aminobenzyloxy)-6-methoxy-3-methoxy-carbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-6-methoxy-3-methoxycarbonyl-7-(4-pyridylmethyl-oxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(2-benzimidazolylmethyloxy)-6-methoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(3,5-diaminobenzyloxy)-6-methoxy-3-methoxy-carbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-6-methoxy-3-

methoxycarbonyl-7-(2-pyridylmethyloxy)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-6-methoxy-3-methoxycarbonyl-7-(3-pyridylmethyloxy)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-6-methoxy-3-methoxycarbonyl-7-(4-pyridylmethyloxy)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-7-(2-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-7-(3-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-7-(4-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(2,5-dimethoxybenzyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(3,5-dimethoxybenzyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-3-methoxy-carbonyl-7-(2-pyridylmethyloxy)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-3-methoxy-carbonyl-7-(3-pyridylmethyloxy)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxyphenyl)-3-methoxy-carbonyl-7-(4-pyridylmethyloxy)-1(2H)-isoquinolinone;

7-(3-aminobenzyloxy)-2-(4-aminophenyl)-4-(4-bromo-3,5-dimethoxy-phenyl)-3-methoxycarbonyl-1(2H)-isoquinolinone;

2-(4-aminophenyl)-4-(4-chloro-3,5-dimethoxyphenyl)-3-methoxy-carbonyl-7-(2-pyridylmethyloxy)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-4-(4-chloro-3,5-dimethoxyphenyl)-3-methoxycarbonyl-7-(3-pyridylmethyloxy)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(3-dimethylaminobenzyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-7-pyrazinylmethyloxy-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(3,5-diaminobenzyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(6-hydroxymethyl-2-pyridylmethyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(4-carboxybenzyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(3-carboxybenzyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-7-[4-(4-methylpiperazinylcarbonyl)benzyloxy]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-7-[3-(4-methylpiperazinylcarbonyl)benzyloxy]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-7-[3-(methylamino)benzyloxy]-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(2-hydroxymethylbenzyloxy)-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-7-(N-oxo-2-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-8-(2-pyridylmethyloxy)-4-(3,4,5-

trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-8-(3-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-8-(4-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-4-(4-chloro-3,5-dimethoxyphenyl)-7-(6-hydroxymethyl-2-pyridylmethyloxy)-3-methoxycarbonyl-1(2H)-isoquinolinone;

2-(4-aminophenyl)-4-(4-chloro-3,5-dimethoxyphenyl)-3-methoxycarbonyl-7-pyrazinylmethyloxy)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-7-(4-pyridylmethyloxy)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-7-(3-pyridylmethyloxy)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-7-(2-pyridylmethyloxy)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(3,5-diaminobenzyloxy)-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(6-hydroxymethyl-2-pyridylmethyloxy)-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(3-methylaminobenzyloxy)-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-7-(2-hydroxymethylaminobenzyloxy)-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-1(2H)-isoquinolinone;

2-(4-aminophenyl)-3-methoxycarbonyl-4-(3,5-dimethoxy-4-methylphenyl)-7-(2-pyrazinylmethyloxy)-1(2H)-isoquinolinone;

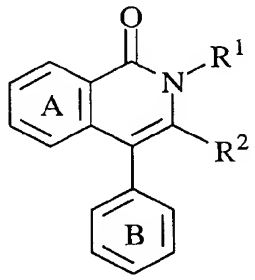
2-(4-aminophenyl)-4-(4-chloro-3,5-dimethoxyphenyl)-3-methoxy-carbonyl-7-(4-pyridylmethyloxy)-1(2H)-isoquinolinone,
or a pharmaceutically acceptable salt thereof.

21. 2-(4-Aminophenyl)-6,7-dimethoxy-3-methoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone or a pharmaceutically acceptable salt thereof.

22. 6,7-Dimethoxy-3-methoxycarbonyl-2-morpholino-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone or a pharmaceutically acceptable salt thereof.

23. 2-(4-Aminophenyl)-3-methoxycarbonyl-7-(2-pyridylmethyloxy)-4-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone or a pharmaceutically acceptable salt thereof.

24. A process for preparing an isoquinolinone derivative of the formula (I):

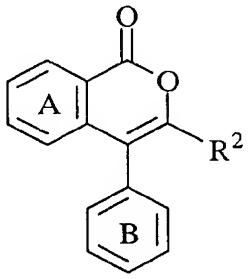


(I)

wherein Ring A and Ring B are the same or different and each a substituted or unsubstituted benzene ring, R^1 is (1) a hydrogen atom, (2) a substituted or unsubstituted lower alkyl group, (3) a substituted or unsubstituted cyclo-lower alkyl group, (4) a substituted or unsubstituted aryl group, (5) a substituted or unsubstituted heterocyclic group, or (6) an amino group optionally having one

or two substituents, R^2 is a group of the formula $-COOR^3$ or $-CON(R^4)(R^5)$, R^3 is a hydrogen atom or an ester residue, and a group of the formula $-N(R^4)(R^5)$ is a substituted or unsubstituted nitrogen-containing aliphatic heterocyclic group or a substituted or unsubstituted amino group, provided that when R^1 is a hydrogen atom or a substituted or unsubstituted lower alkyl group, then at least one of Ring A and Ring B is a benzene ring which is substituted by two or more lower alkoxy groups, or a pharmaceutically acceptable salt thereof,

which comprises reacting an isocoumarin derivative of the formula (II):



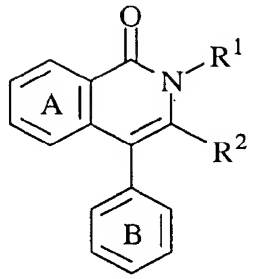
(II)

wherein the symbols are the same as defined above, or a salt thereof, with an amine compound of the formula (III):

$$R^1-NH_2 \qquad \text{(III)}$$

wherein R^1 is the same as defined above, or a salt thereof, and if necessary, followed by converting the product into a pharmaceutically acceptable salt thereof.

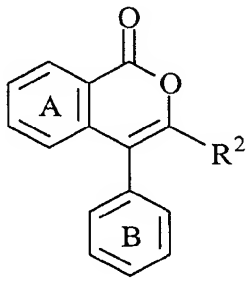
25. A process for preparing an isoquinolinone derivative of the formula (I):



(I)

wherein Ring A and Ring B are the same or different and each a substituted or unsubstituted benzene ring, R^1 is (1) a hydrogen atom, (2) a substituted or unsubstituted lower alkyl group, (3) a substituted or unsubstituted cyclo-lower alkyl group, (4) a substituted or unsubstituted aryl group, (5) a substituted or unsubstituted heterocyclic group, or (6) an amino group optionally having one or two substituents, R^2 is a group of the formula $-COOR^3$ or $-CON(R^4)(R^5)$, R^3 is a hydrogen atom or an ester residue, and a group of the formula $-N(R^4)(R^5)$ is a substituted or unsubstituted nitrogen-containing aliphatic heterocyclic group or a substituted or unsubstituted amino group, provided that when R^1 is a hydrogen atom or a substituted or unsubstituted lower alkyl group, then at least one of Ring A and Ring B is a benzene ring which is substituted by two or more lower alkoxy groups, or a pharmaceutically acceptable salt thereof,

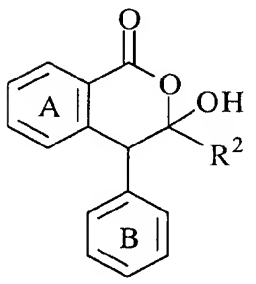
which comprises subjecting an isocoumarin derivative of the formula (II):



(II)

wherein the symbols are the same as defined above, or a salt thereof, to

hydrolysis to give a compound of the formula (IV):



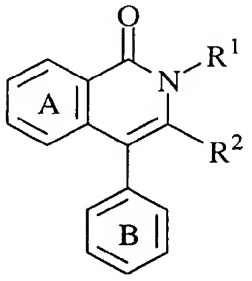
(IV)

wherein the symbols are the same as defined above, further reacting the compound (IV) with an amine compound of the formula (III):

$$R^1\text{–}NH_2 \qquad \text{(III)}$$

wherein R^1 is the same as defined above, or a salt thereof, if necessary, followed by converting the product into a pharmaceutically acceptable salt thereof.

26. A process for preparing an isoquinolinone derivative of the formula (I):

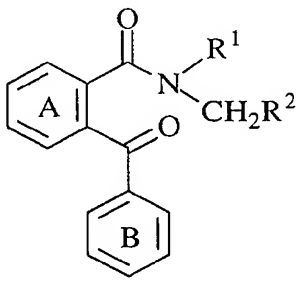


(I)

wherein Ring A and Ring B are the same or different and each a substituted or unsubstituted benzene ring, R^1 is (1) a hydrogen atom, (2) a substituted or unsubstituted lower alkyl group, (3) a substituted or unsubstituted cyclo-lower alkyl group, (4) a substituted or unsubsituted aryl group, (5) a substituted or unsubstituted heterocyclic group, or (6) an amino group optionally having one or two substituents, R^2 is a group of the formula –$COOR^3$ or –$CON(R^4)(R^5)$, R^3

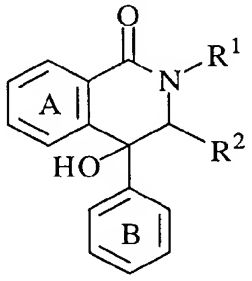
is a hydrogen atom or an ester residue, and a group of the formula $-N(R^4)(R^5)$ is a substituted or unsubstituted nitrogen-containing aliphatic heterocyclic group or a substituted or unsubstituted amino group, provided that when R^1 is a hydrogen atom or a substituted or unsubstituted lower alkyl group, then at least one of Ring A and Ring B is a benzene ring which is substituted by two or more lower alkoxy groups, or a pharmaceutically acceptable salt thereof,

which comprises subjecting a benzoylbenzamide compound of the formula (V):



(V)

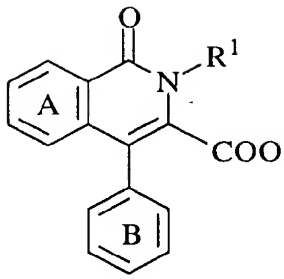
wherein the symbols are the same as defined above, or a salt thereof, to intramolecular cyclization reaction, to give a compound of the formula (VI):



(VI)

wherein the symbols are the same as defined above, further subjecting the compound (VI) to dehydration reaction, and if necessary, followed by converting the product into a pharmaceutically acceptable salt thereof.

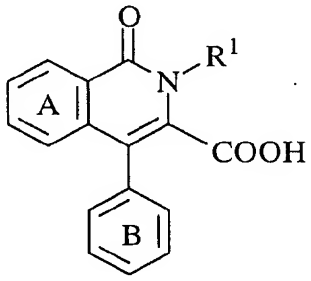
27. A process for preparing an isoquinolinone derivative of the formula (I-b):



(I-b)

wherein Ring A and Ring B are the same or different and each a substituted or unsubstituted benzene ring, R^1 is (1) a hydrogen atom, (2) a substituted or unsubstituted lower alkyl group, (3) a substituted or unsubstituted cyclo-lower alkyl group, (4) a substituted or unsubsituted aryl group, (5) a substituted or unsubstituted heterocyclic group, or (6) an amino group optionally having one or two substituents, and R^{31} is an ester residue, provided that when R^1 is a hydrogen atom or a substituted or unsubstituted lower alkyl group, then at least one of Ring A and Ring B is a benzene ring which is substituted by two or more lower alkoxy groups, or a pharmaceutically acceptable salt thereof,

which comprises subjecting a compound of the formula (I-a):

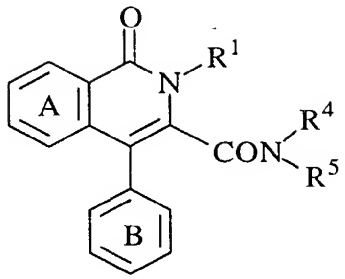


(I-a)

wherein the symbols are the same as defined above, to esterification reaction, and if necessary, followed by converting the product into a pharmaceutically acceptable salt thereof.

28. A process for preparing an isoquinolinone derivative of the

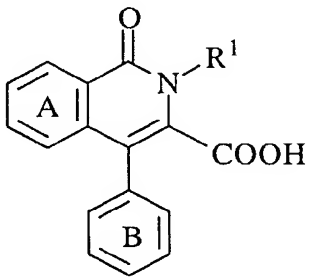
formula (I-c):



(I-c)

wherein Ring A and Ring B are the same or different and each a substituted or unsubstituted benzene ring, R^1 is (1) a hydrogen atom, (2) a substituted or unsubstituted lower alkyl group, (3) a substituted or unsubstituted cyclo-lower alkyl group, (4) a substituted or unsubsituted aryl group, (5) a substituted or unsubstituted heterocyclic group, or (6) an amino group optionally having one or two substituents, and a group of the formula $-N(R^4)(R^5)$ is a substituted or unsubstituted nitrogen-containing aliphatic heterocyclic group, or a substituted or unsubstituted amino group, provided that when R^1 is a hydrogen atom or a substituted or unsubstituted lower alkyl group, then at least one of Ring A and Ring B is a benzene ring which is substituted by two or more lower alkoxy groups, or a pharmaceutically acceptable salt thereof,

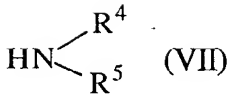
which comprises reacting a compound of the formula (I-a):



(I-a)

wherein the symbols are the same as defined above, with an amine compound of

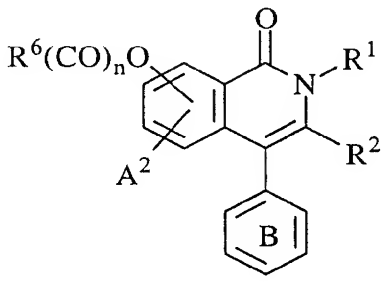
the formula (VII):



(VII)

wherein the symbols are the same as defined above, or a salt thereof, if necessary, followed by converting the product into a pharmaceutically acceptable salt thereof.

29. A process for preparing an isoquinolinone derivative of the formula (I-e):

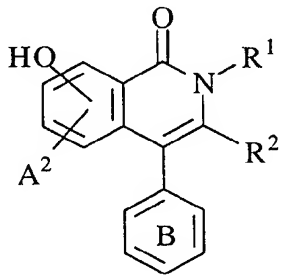


(I-e)

wherein Ring B is a substituted or unsubstituted benzene ring, A^2 is a hydrogen atom, a protected or unprotected hydroxy group, a lower alkylenedioxy group, a halogen atom, a lower alkyl group, a mono- or di-lower alkylcarbamoyloxy group or a lower alkoxy group, R^1 is (1) a hydrogen atom, (2) a substituted or unsubstituted lower alkyl group, (3) a substituted or unsubstituted cyclo-lower alkyl group, (4) a substituted or unsubsituted aryl group, (5) a substituted or unsubstituted heterocyclic group, or (6) an amino group optionally having one or two substituents, R^2 is a group of the formula $-COOR^3$ or $-CON(R^4)(R^5)$, R^3 is a hydrogen atom or an ester residue, a group of the formula $-N(R^4)(R^5)$ is a substituted or unsubstituted nitrogen-containing aliphatic heterocyclic group, or a substituted or unsubstituted amino group, R^6 is a substituted or

unsubstituted lower alkyl group, a substituted or unsubstituted lower alkenyl group, a substituted or unsubstituted cyclo-lower alkyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted arylsulfonyl group, or a substituted or unsubstituted heterocyclic group, and n is 0 or 1, provided that when R^1 is a hydrogen atom or a substituted or unsubstituted lower alkyl group, then at least one of Ring A and Ring B is a benzene ring which is substituted by two or more lower alkoxy groups, or a pharmaceutically acceptable salt thereof,

which comprises reacting a compound of the formula (I-d):



(I-d)

wherein the symbols are the same as defined above, or a salt thereof, with a compound of the formula (VIII-a):

$$R^6\text{–}COOH \qquad \text{(VIII-a)}$$

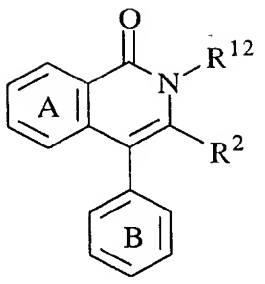
wherein R^6 is the same as defined above, or a reactive derivative thereof, or with a compound of the formula (VIII-b):

$$R^6\text{–}X \qquad \text{(VIII-b)}$$

wherein X is a leaving group, and R^6 is the same as defined above, and if necessary, followed by converting the product into a pharmaceutically acceptable salt thereof.

30. A process for preparing an isoquinolinone derivative of the

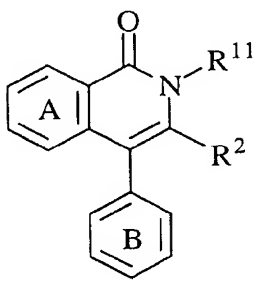
formula (I-g):



(I-g)

wherein Ring A and Ring B are the same or different and each a substituted or unsubstituted benzene ring, R^{12} is an amino-substituted lower alkyl group, an amino-substituted cyclo-lower alkyl group, an amino-substituted aryl group, an amino-substituted heterocyclic group, or an amino group, R^2 is a group of the formula $-COOR^3$ or $-CON(R^4)(R^5)$, and R^3 is a hydrogen atom or an ester residue, and a group of the formula $-N(R^4)(R^5)$ is a substituted or unsubstituted nitrogen-containing aliphatic heterocyclic group or a substituted or unsubstituted amino group, provided that when R^{12} is an amino-substituted lower alkyl group, then at least one of Ring A and Ring B is a benzene ring which is substituted by two or more lower alkoxy groups, or a pharmaceutically acceptable salt thereof,

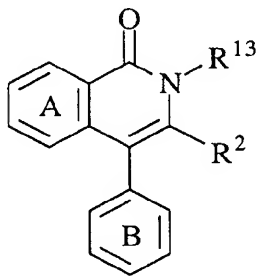
which comprises removing a protecting group for amino group from a compound of the formula (I-f):



(I-f)

wherein R^{11} is a lower alkyl group substituted by a protected amino group, a cyclo-lower alkyl group substituted by a protected amino group, an aryl group substituted by a protected amino group, a heterocyclic group substituted by a protected amino group, or a protected amino group, and the other symbols are the same as defined above, or a salt thereof, and if necessary, followed by converting the product into a pharmaceutically acceptable salt thereof.

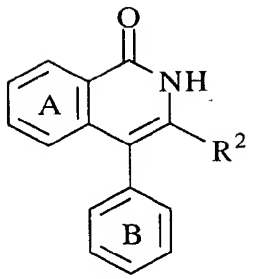
31. A process for preparing an isoquinolinone derivative of the formula (I-i):



(I-i)

wherein Ring A and Ring B are the same or different and each a substituted or unsubstituted benzene ring, R^{13} is a substituted or unsubstituted lower alkyl group, R^2 is a group of the formula $-COOR^3$ or $-CON(R^4)(R^5)$, and R^3 is a hydrogen atom or an ester residue, and a group of the formula $-N(R^4)(R^5)$ is a substituted or unsubstituted nitrogen-containing aliphatic heterocyclic group or a substituted or unsubstituted amino group, provided that at least one of Ring A and Ring B is a benzene ring which is substituted by two or more lower alkoxy groups, or a pharmaceutically acceptable salt thereof,

which comprises reacting a compound of the formula (I-h):



(I-h)

wherein the symbols are the same as defined above, or a salt thereof, with a compound of the formula (IX):

$$R^{13}\text{–}X^1 \qquad \text{(IX)}$$

wherein X^1 is a halogen atom, and R^{13} is the same as defined above, and if necessary, followed by converting the product into a pharmaceutically acceptable salt thereof.

32. A pharmaceutical composition which comprises a therapeutically effective amount of a compound as set forth in any one of claims 1 to 23 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent thereto.

33. The pharmaceutical composition according to claim 32, which is a medicament for treating erectile dysfunction in mammals including human species.

34. A method for treatment and/or prophylaxis of chronic heart failure, angina, erectile dysfunction, female sexual dysfunction, hypertension, pulmonary hypertension, atherosclerosis or restrenosis after percutaneous transluminal coronary angioplasty in mammal, which comprises administering to the mammal a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof as set forth in any one of claims 1 to 23.

35. A use of an isoquinolinone derivative as set forth in any one of claims 1 to 23 in the manufacture of a pharmaceutical composition for the treatment and/or prophylaxis of chronic heart failure, angina, erectile dysfunction, female sexual dysfunction, hypertension, pulmonary hypertension, atherosclerosis or restrenosis after percutaneous transluminal coronary angioplasty.

INTERNATIONAL SEARCH REPORT

Int .tional Application No
PCT/JP 98/00715

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D217/26 A61K31/47 C07D401/12 C07D409/12 C07D401/04
C07D401/06 C07D405/04 C07D405/06 C07D491/04 C07D413/04
C07D401/10 C07D405/12 //(C07D491/04,317:00,221:00)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 634 402 A (TAKEDA CHEMICAL INDUSTRIES LTD) 18 January 1995 see claims	1,32-35
A	EP 0 585 913 A (TAKEDA CHEMICAL INDUSTRIES LTD) 9 March 1994 see claims	1,32-35
A	EP 0 490 823 A (SANDOZ LTD) 17 June 1992 see the whole document	1,32-35
A	FR 2 502 619 A (MARUKO SEIYAKU CO.,LTD) 1 October 1982 see claims	1,32-35

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
28 April 1998	04. 05. 98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Henry, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Ir ational application No.
PCT/JP 98/ 00715

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 34 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In. ational Application No
PCT/JP 98/00715

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0634402 A	18-01-95	CA 2128055 A	15-01-95
		JP 7076573 A	20-03-95
		US 5527811 A	18-06-96
EP 0585913 A	09-03-94	AT 161530 T	15-01-98
		AU 667739 B	04-04-96
		AU 4613293 A	10-03-94
		CA 2105518 A	05-03-94
		CN 1090274 A	03-08-94
		DE 69315920 D	05-02-98
		FI 933857 A	17-05-94
		HU 67284 A	28-03-95
		JP 7010844 A	13-01-95
		NO 933133 A,B,	07-03-94
		NZ 248583 A	27-04-95
		US 5482967 A	09-01-96
		US 5700810 A	23-12-97
EP 0490823 A	17-06-92	AT 145201 T	15-11-96
		AU 643575 B	18-11-93
		AU 8898591 A	18-06-92
		CA 2057524 A	14-06-92
		CS 9103757 A	17-06-92
		DE 69123124 D	19-12-96
		DE 69123124 T	15-05-97
		ES 2093694 T	01-01-97
		FI 915844 A	14-06-92
		IL 100328 A	08-12-95
		JP 2042806 C	09-04-96
		JP 4275276 A	30-09-92
		JP 7064820 B	12-07-95
		MX 9102502 A	01-06-92
		PL 168329 B	29-02-96
		PT 99775 A	30-11-92
		RU 2060992 C	27-05-96
		US 5177085 A	05-01-93
		ZA 9109858 A	14-06-93
FR 2502619 A	01-10-82	JP 58150564 A	07-09-83
		JP 57159770 A	01-10-82

INTERNATIONAL SEARCH REPORT

Information on patent family members

In ational Application No
PCT/JP 98/00715

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 2502619 A		CH 648022 A	28-02-85
		DE 3211501 A	02-12-82
		GB 2098980 A,B	01-12-82
		NL 8201264 A	18-10-82
		US 4443607 A	17-04-84
		AU 8211382 A	07-10-82